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(21) International Application Number: PCT/US97/00997 (22) International Filing Date: 22 January 1997 (22.01.97) (30) Priority Data: 60/010,287 22 January 1996 (22.01.96) US (71) Applicant (for all designated States except US): ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): HOLLINSHEAD, Sean, P. [GB/US]; 1201 North Street, Durham, NC 27701 (US). HUFF, Bret, E. [US/US]; 201 Oak Hill Lane, Mooresville, IN 46158 (US). HUGHES, Philip, F. [US/US]; 627 Arlington Street, Chapel Hill, NC 27514 (US). MENDOZA, Jose, S. [MX/US]; 5302-G Penrith Drive, Durham, NC 27713 (US). MITCH, Charles, H. [US/US]; 3210 Grove Parkway, Columbus, IN 47203 (US). STASZAK, Michael, A. [US/US]; 4515 North Lakeridge Drive, Indianapolis, IN 46234 (US). WARD, John, S. [US/US]; 241 East Brunswick Avenue, Indianapolis, IN 46227 (US). WILSON, Joseph, W.	[US/US]; 5405 Fortune's Ridge Drive, Durham, NC 27713 (US). (74) Agents: VORNDRAN-JONES, MaCharri et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US). (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>	
(54) Title: INDANE DERIVATIVES FOR ANTIPSYCHOTIC COMPOSITIONS (57) Abstract <p>The present invention provides novel indane-like compounds which can be useful for treating psychosis and other conditions associated with the modulation of a muscarinic receptor. The invention provides formulations and methods for using the novel compounds.</p>		

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" INDANE DERIVATIVES FOR ANTIPSYCHOTIC COMPOSITIONS"

5

The present invention relates to novel indane-like compounds and to formulations containing such indane-like compounds as an active ingredient for pharmaceutical or
10 veterinary use.

Currently there are many drugs available for the treatment of disorders of the central nervous system. Amongst these drugs is a category known as antipsychotics
15 for treating serious mental conditions such as psychosis, including but not limited to schizophrenia and schizophreniform illnesses. The skilled artisan will recognize that these psychotic conditions are characterized by hallucinations, delusions, or grossly disorganized
20 behavior which indicate that the patient suffers from gross impairment in reality testing. Drugs having said antipsychotic activity can be useful for treating a variety of important psychotic disorders. The drugs commercially available for such conditions are often associated with
25 undesirable side effects. There is a need for additional therapeutic choices to control or eliminate the symptoms in the safest and most effective way. Furthermore, patients often do not respond or only partially respond to present drug treatment, and estimates of such partial- or non-
30 responders has varied between 40% and 80% of those treated.

Ever since antipsychotics were introduced it has been observed that patients are liable to suffer from drug-induced extrapyramidal symptoms which include drug-induced Parkinsonism, acute dystonic reactions, akathisia, tardive
35 dyskinesia and tardive dystonia. The Simpson Angus Scale, Barnes Akathisia Rating Scale and Abnormal Involuntary Movement Scale (AIMS) are well known scales for assessing

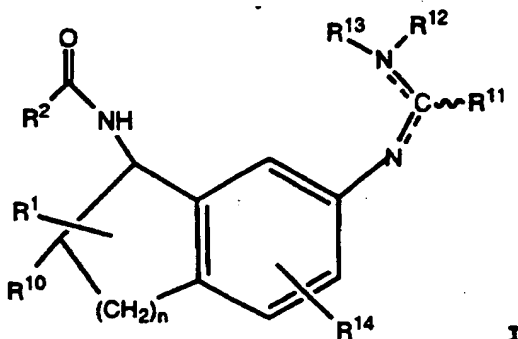
extrapyramidal symptoms. The great majority of drugs available for treatment of schizophrenia are prone to produce these extrapyramidal side effects when used at dosages that yield a beneficial effect on the symptoms of the disease. The severity of adverse events and/or lack of efficacy in a considerable number of patients frequently results in poor compliance or termination of treatment.

Many of the drugs are associated with a sedative effect and may also have an undesirable influence on the affective symptoms of the disease, causing depression. In some instances long term use of the drug leads to irreversible conditions, such as the tardive dyskinesia and tardive dystonia referred to supra.

A widely-used antipsychotic, haloperidol, is one such drug, which has been reported as causing a high incidence of extrapyramidal symptoms and may also cause tardive dyskinesia. More recently, clozapine, one of a large group of heterocyclic antipsychotics, has been introduced with the claim that it is free from extrapyramidal effects. However, the compound was found to cause agranulocytosis in some patients, a condition resulting in a lowered white blood cell count which can be life-threatening, and it may now only be employed under very strict medical observation and supervision.

Therefore, new compounds having antipsychotic activity are highly desired.

The present invention provides a compound of the Formula I:



R^1 is selected from the group consisting of hydrogen, $-OR^4$, $-SR^5$, C_1-C_3 alkyl, C_2-C_3 alkenyl, halo, $-CN$, $S(O)_{m2}$, $-COR^{4b'}$, and $-OC(O)-R^{15}$;

5 $m2$ is from 0 to 2;

R^2 is selected from the group consisting of C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, C_2-C_{10} alkenyl, substituted C_2-C_{10} alkenyl, C_3-C_8 cycloalkyl, substituted C_3-C_8 cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic;

R^4 is hydrogen, C_1-C_3 alkyl;

R^5 is hydrogen, C_1-C_3 alkyl;

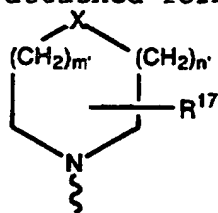
R^{10} is selected from the group consisting of hydrogen, carbonyl, halo, and C_1-C_3 alkyl;

15 R^{11} is selected from the group consisting of hydrogen and C_1-C_3 alkyl;

R^{12} is independently selected from the group consisting of hydrogen, C_1-C_{10} alkyl, and aryl;

20 R^{13} is independently selected from the group consisting of hydrogen, C_1-C_{10} alkyl, and aryl; or

R^{12} and R^{13} together with the nitrogen to which they are attached form a group of the formula II:



II; or

25 II' wherein the II' group is a group of Formula II which is unsaturated; or

R^{11} and R^{12} together with the nitrogen and carbon to which they are bound can join to form a three to six membered ring;

R^{14} is selected from the group consisting of H, halo, C_1-C_3 alkyl, $S(O)_{m3}$ and $-OR^{16}$;

30 R^{15} is C_1-C_3 alkyl or aryl;

R^{16} is C_1-C_3 alkyl;

R¹⁷ is independently selected from the group consisting of hydrogen, -OR^{4'}, -SR^{5'}, C₁-C₃ alkyl, C₂-C₃ alkenyl, halo, -CN, S(O)_{m2'}, -COR^{4b}, and -OC(O)-R^{15'};

R^{4b} and R^{4b'} are each independently selected from hydrogen and C₁-C₃ alkyl;

R^{15'} is C₁-C₃ alkyl or aryl;

m_{2'} is 0 to 2;

R^{4'} is hydrogen, C₁-C₃ alkyl;

R^{5'} is hydrogen, C₁-C₃ alkyl;

m₂ is 0 to 2;

X is selected from the group consisting of C, O, S, N, carbonyl, and a bond;

n' is 0 to 2;

m' is 0 to 2;

m₃ is 0 to 2;

n is 0 to 3; or

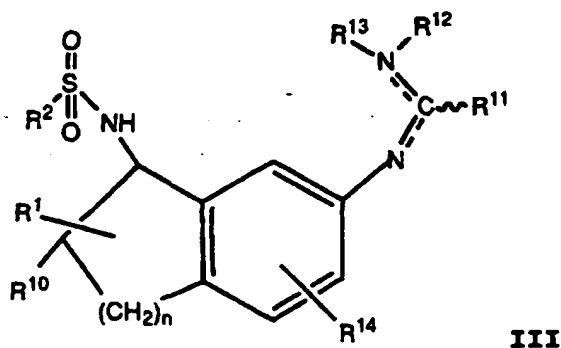
a pharmaceutically acceptable salt or solvate thereof.

Further, the invention provides a method for treating psychosis comprising administering a compound of Formula I to a mammal in need of such treatment.

Additionally, the present invention provides a method for interacting with a muscarinic receptor comprising administering a compound of Formula I.

Finally, the invention provides a formulation containing a compound of Formula I as an active ingredient.

Further this invention provides compounds of the Formula III



-5-

R^1 is selected from the group consisting of hydrogen, $-OR^4$, $-SR^5$, C_1-C_3 alkyl, C_2-C_3 alkenyl, halo, $-CN$, $S(O)_{m2}$, $-COR^{4b'}$, and $-OC(O)-R^{15}$;

$m2$ is from 0 to 2;

5 R^2 is selected from the group consisting of C_1-C_{10} alkyl, substituted C_1-C_{10} alkyl, C_2-C_{10} alkenyl, substituted C_2-C_{10} alkenyl, C_3-C_8 cycloalkyl, substituted C_3-C_8 cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic;

10 R^4 is hydrogen, C_1-C_3 alkyl;

R^5 is hydrogen, C_1-C_3 alkyl;

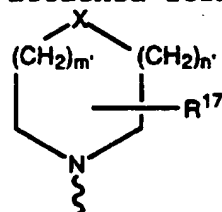
R^{10} is selected from the group consisting of hydrogen, carbonyl, halo, and C_1-C_3 alkyl;

15 R^{11} is selected from the group consisting of hydrogen and C_1-C_3 alkyl;

R^{12} is independently selected from the group consisting of hydrogen, C_1-C_{10} alkyl, and aryl;

R^{13} is independently selected from the group consisting of hydrogen, C_1-C_{10} alkyl, and aryl; or

20 R^{12} and R^{13} together with the nitrogen to which they are attached form a group of the formula II:



II; or

II' wherein the II' group is a group of Formula II which is unsaturated; or

25 R^{11} and R^{12} together with the nitrogen and carbon to which they are bound can join to form a three to six membered ring;

R^{14} is selected from the group consisting of H, halo, C_1-C_3 alkyl, $S(O)_{m3}$ and $-OR^{16}$;

R^{15} is C_1-C_3 alkyl or aryl;

30 R^{16} is C_1-C_3 alkyl;

R^{17} is independently selected from the group consisting of hydrogen, $-OR^{4'}$, $-SR^{5'}$, C_1 - C_3 alkyl, C_2 - C_3 alkenyl, halo, $-CN$, $S(O)_{m2'}$, $-COR^{4b}$, and $-OC(O)-R^{15'}$;

R^{4b} and $R^{4b'}$ are each independently selected from hydrogen and C_1 - C_3 alkyl;

$R^{15'}$ is C_1 - C_3 alkyl or aryl;

$m2'$ is 0 to 2;

$R^{4'}$ is hydrogen, C_1 - C_3 alkyl;

$R^{5'}$ is hydrogen, C_1 - C_3 alkyl;

$m2$ is 0 to 2;

X is selected from the group consisting of C, O, S, N, carbonyl, and a bond;

n' is 0 to 2;

m' is 0 to 2;

$m3$ is 0 to 2;

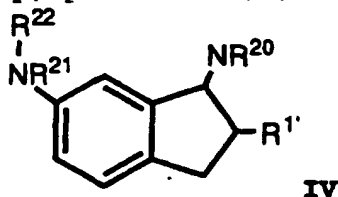
n is 0 to 3; or

a pharmaceutically acceptable salt or solvate thereof.

Additionally, this invention provides a formulation comprising a compound of Formula III and one or more pharmaceutically acceptable excipients or carriers therefor.

Also included is a method for treating a condition associated with the modulation of a muscarinic receptor comprising administering an effective amount of a compound of Formula III to a mammal in need of such treatment.

Additionally, provided is a compound of Formula IV



R^{21} and R^{22} are selected from H and O;

R^{20} is selected from amine protecting groups;

$R^{1'}$ is selected from the group consisting of $-OR^{4'}$, $-SR^{5'}$, C_1 - C_3 alkyl, C_2 - C_3 alkenyl, halo, $-CN$, $S(O)_{m2}$, $-COR^{4b'}$, and $-OC(O)-R^{15}$;

$m2$ is 0 to 2;

R⁴ and R^{4b'} are each independently selected from hydrogen and C₁-C₃ alkyl;

R⁵ is selected from hydrogen and C₁-C₃ alkyl;

R¹⁵ is C₁-C₃ alkyl or aryl;

5 or

a pharmaceutically acceptable salt or solvate thereof.

Detailed Description of the Invention

The term "treating" as used herein includes
10 prophylaxis of the named physical and/or mental condition or amelioration or elimination of the developed physical and/or mental condition once it has been established.

The substituent of Formula II can be from a 3-member to 8 member ring. The substituent of Formula II' is
15 unsaturated. Formula II' is optionally aromatic, but is in no way required to be aromatic. It may be preferred that Formula II' contains from one to two double bonds.

The term "interacting with a muscarinic receptor" refers to a compound acting as a muscarinic receptor agonist,
20 antagonist, or partial agonist. Most preferably, the compounds of this invention will act as an agonist of a muscarinic receptor. It is especially preferred that a compound of this invention will selectively interact with a m4 muscarinic receptor subtype. Further it is particularly
25 preferred that a compound of this invention will act as a selective m4 muscarinic receptor agonist.

The terms "C₁-C_m alkyl" wherein m= 2-10, as used herein, represent a branched or linear alkyl group having
30 from one to the specified number of carbon atoms. For example, typical C₁-C₆ alkyl groups include methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl and the like.

The term "substituted C₁-C_m alkyl" refers to an alkyl group which is substituted with from one to five
35 selected from the group consisting of C₂-C₆ alkenyl, halo, -CF₃, -OR^{4a}, -SR^{5a}, -CO₂R^{6a}, halo, C₃-C₈ cycloalkyl, substituted C₄-C₈ cycloalkyl, and -CN; wherein 4a, 5a, and 6a

are each independently selected from the group consisting of hydrogen, C₁-C₃ alkyl, aryl and substituted aryl.

The term "carbonyl" has the meaning commonly attributed to the term by the skilled artisan. For example,
5 =O.

The terms "C₂-C_n alkenyl" wherein n= 3-10, as used herein, represents an olefinically unsaturated branched or linear group having from 2 to 10 carbon atoms and at least one double bond. The groups can be branched or straight
10 chain. Examples of such groups include 1-propenyl, 2-propenyl (-CH₂-CH=CH₂), 1-butenyl (-CH=CHCH₂CH₃), 1,3-butadienyl (-CH=CHCH=CH₂), hexenyl, pentenyl, and the like.

The terms "halide", "halogen", and "halo" include fluorine, chlorine, bromine, and iodine. The preferred
15 halogen is chlorine.

The term "C₃-C_n cycloalkyl" wherein n=4-8, represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like.

The term "heterocyclic" refers to a heterocyclic
20 ring having from four to eight members and from one to three non-carbon atoms selected from the group consisting of N, O, and S; or a combination thereof, and which heteroaryl group is optionally fused with a phenyl group.

The term "substituted heterocyclic" refers to a
25 heterocyclic group which may be substituted with from one to three substituents selected from the group consisting of halogen(s), -CF₃, NO₂, -CN, C₁-15-alkyl, C₂-5-alkenyl, C₂-5-alkynyl, -COR^{6a}, -OR^{4a}, -SR^{5a}, C₃-C₈ cycloalkyl, C₅-C₈ cycloalkenyl, substituted C₃-C₈ cycloalkyl, substituted C₅-C₈
30 cycloalkenyl, and aryl; wherein 4a, 5a, and 6a are each independently selected from hydrogen, -CF₃, C₁-C₃ alkyl, aryl, and -C₁-C₃ alkyl-aryl.

As used herein the term "amine protecting group" refers to protecting groups such as those discussed in
35 Theodora W. Greene, Protective Groups in Organic Synthesis, (Wiley, 1981) pp. 218-287. Especially preferred amine

protecting groups are carbamates. One particularly preferred amine protecting group is BOC.

The term "substituted(C₅-C_n) cycloalkyl" refers to a cycloalkyl group as described supra wherein the cycloalkyl group may be substituted with from one to four substituents independently selected from the group consisting of hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, NO₂, halo, halo(C₁-C₆)alkyl, halo(C₂-C₆)alkenyl, C₂-C₆ alkenyl, C₃-C₈ cycloalkyl-(C₁-C₃)alkyl, C₅-C₈ cycloalkenyl, C₅-C₈ cycloalkenyl-(C₁-C₃)alkyl, COR_{5a}, C₁-C₁₀ alkanoyl, C₇-C₁₆ arylalkyl, CO₂R_{5a}, (C₁-C₆ alkyl)_mamino, -SR_{5a}, and OR_{5a}; wherein 5a is selected from hydrogen and C₁-C₃ alkyl; m is from one to two.

The term "C₃-C₈ cycloalkyl-(C₁-C₃)alkyl" represents a linear alkyl group substituted at a terminal carbon with a C₃-C₈ cycloalkyl group. Typical cycloalkylalkyl groups include cyclohexylethyl, cyclohexylmethyl, 3-cyclopentylpropyl, and the like.

The term "C₅-C₈ cycloalkenyl" represents an olefinically unsaturated ring having five to eight carbon atoms, eg., cyclohexadienyl, cyclohexenyl, cyclopentenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, cycloheptadienyl, cyclooctatrienyl and the like. The cycloalkenyl group may be substituted with from one to four substituents selected from the group consisting of hydrogen, C₁-C₆ alkyl, NO₂, halo, halo(C₁-C₆)alkyl, halo(C₂-C₆)alkenyl, C₂-C₆ alkenyl, (C₁-C₆ alkyl)_mamino, COR₅, C₁-C₁₀ alkanoyl, OR₅, CO₂R₅, -SR₅, and C₇-C₁₆ arylalkyl.

The term "C₅-C₈ cycloalkenyl-(C₁-C₃)alkyl" represents a linear C₁-C₃ alkyl group substituted at a terminal carbon with a C₅-C₈ alkenyl group.

As used herein the term "carboxy" refers to a substituent having the common meaning understood by the skilled artisan, wherein the point of attachment may be through the carbon or oxygen atom of the group.

As used herein the term "aryl" means an organic radical derived from an aromatic hydrocarbon by the removal of one atom. For example, the term includes, but is in no

way limited to biphenyl, phenyl or naphthyl. The term "aryl" refers to hydrocarbon aryl groups. Most preferably, aryl refers to C₆-C₁₀ aryl, wherein the aryl ring system, including any alkyl substitutions, comprises from 6 to 10 carbon atoms; e.g., phenyl, 3,3-dimethylphenyl, naphthyl, and the like. The aryl radical may be substituted by one or two C₁-C₆ straight or branched alkyl. The aryl group may be fused with a heteroaryl or heterocyclic.

"Substituted aryl" refers to an aryl group which may be substituted with from one to three substituents selected from the group consisting of halogen(s), -CF₃, NO₂, -CN, C₁₋₁₅-alkyl, C₂₋₅-alkenyl, C₂₋₅-alkynyl, -COR^{6a}, -OR^{4a}, -SR^{5a}, C₃-C₈ cycloalkyl, C₅-C₈ cycloalkenyl, substituted C₃-C₈ cycloalkyl, substituted C₅-C₈ cycloalkenyl, and aryl; wherein 4a, 5a, and 6a are each independently selected from hydrogen, -CF₃, C₁-C₃ alkyl, aryl, and -C₁-C₃ alkyl-aryl. The substituents may be located at any available position on the ring, provided that there is not more than one substituent selected from the group consisting of aryl, C₃-C₈ cycloalkyl, substituted C₃-C₈ cycloalkyl, C₅-C₈ cycloalkenyl, and substituted C₅-C₈ cycloalkenyl.

As used herein, the phrase "heteroaryl" means an aryl group containing from one to three N, O or S atom(s) or a combination thereof, and which heteroaryl group is optionally fused with a phenyl group. The phrase "heteroaryl" includes, but is not limited to, 5-membered heteroaryls having one hetero atom (e.g. thiophenes, pyrroles, furans); 5-membered heteraryls having two heteroatoms in 1,2 or 1,3 positions (e.g. oxazoles, pyrazoles, imidazoles, thiazoles, purines); 5-membered heteraryls having three heteroatoms (e.g. triazoles, thiadiazoles); 5-membered heteraryls having 3-heteroatoms; 6-membered heteroaryls with one heteroatom (e.g. pyridine, quinoline, isoquinoline, phenanthrine, 5,6-cycloheptenopyridine); 6-membered heteraryls with two heteroatoms (e.g. pyridazines, cinnolines, phthalazines,

pyrazines, pyrimidines, quinazolines); 6-membered heteroaryls with three heteroatoms (e.g. 1,3,5-triazine); and 6-member heteroaryls with four heteroatoms.

5 Particularly preferred are benzothiophenes, pyridines, and furans. Most preferred, the heteroaryl group is a four to eight membered ring.

The term "substituted heteroaryl" refers to a heteroaryl group which is substituted at carbon or nitrogen atom(s) with C₁-6-alkyl, -CF₃, phenyl, benzyl, substituted
10 aryl or thienyl, or a carbon atom in the heteroaryl group together with an oxygen atom form a carbonyl group. Such substituted heteroaryl may optionally be fused with a phenyl group.

The term "C₇-C₁₆ arylalkyl" represents an aryl-(C₁-
15 C₁₀)alkyl substituent wherein the alkyl group is linear, such as but not limited to, benzyl, phenethyl, 3-phenylpropyl, or phenyl-*t*-butyl; or branched. The aryl alkyl moiety is attached to the parent nucleus via the alkyl group.

The term "organic solvent" includes solvents
20 containing carbon, such as halogenated hydrocarbons, ether, toluene, xylene, benzene, and tetrahydrofuran.

The term "agitate" includes such techniques as stirring, centrifugation, mixing, and other similar methods.

The term "ligand" refers to compounds that are
25 bound by the designated receptor. Compounds useful as ligands may be used to occupy the stated receptor site or may act as a selective agonist at the stated receptor site.

The abbreviations used herein have their accepted meaning, unless stated otherwise. Such accepted meaning
30 shall be the meaning attributed to such term by the skilled artisan or the American Chemical Society.

The terms "MeO" and "EtO" refer to methoxy and ethoxy substituents which are bound to the parent molecule through the oxygen.

35 A method for generating the indane scaffold used in this invention for compound forming purposes comprises the following sequential steps:

-12-

1. Nitration of indanone starting yields nitroindanone which is then separated from minor component byproducts.

5 2. The product of step 1 is reduced to give the corresponding alcohol.

3. The product of step 2 is then subjected to an acid catalyzed dehydration to give the corresponding indene.

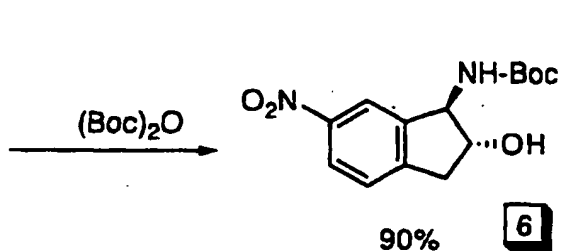
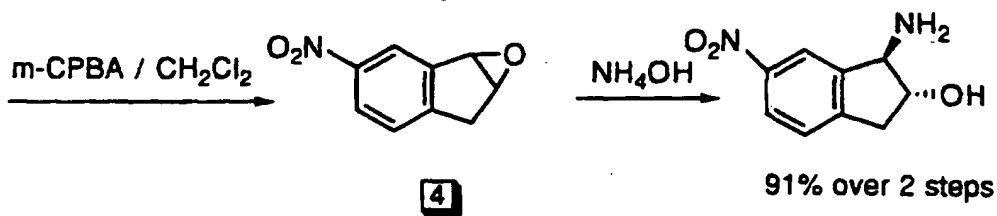
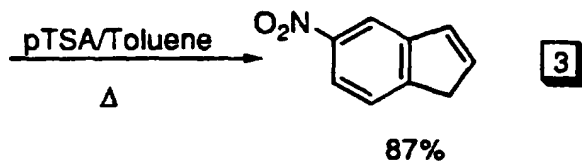
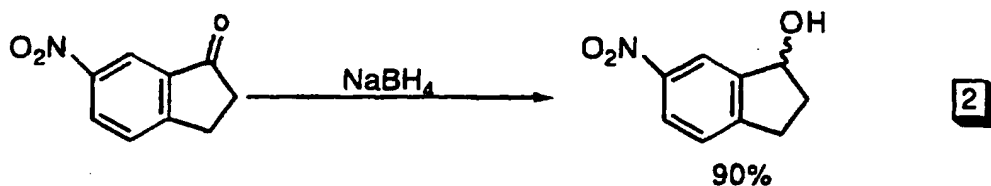
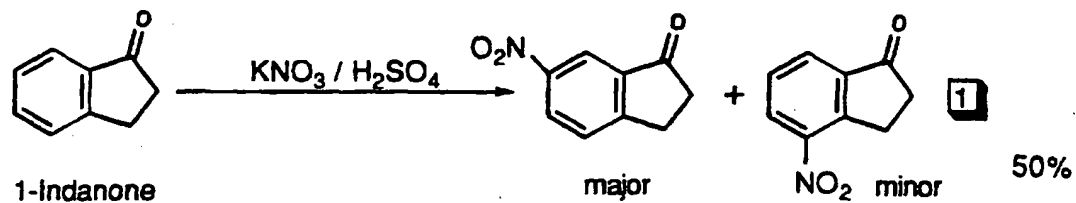
10 4. The double bond of the product of step 3 is oxidized to give the epoxide.

15 5. The product epoxide 4 is then reacted with ammonium hydroxide to give the amino alcohol.

6. The amino alcohol of step 5 is protected with a conventional protecting group.

20 The preceding method of indane scaffold preparation is further illustrated by the following reaction scheme:

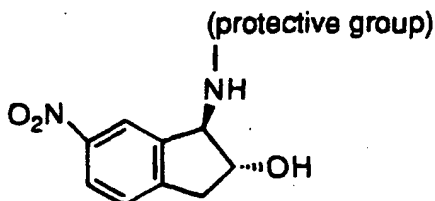
INDAN SCAFFOLD FORMATION



5 The formation of indane compounds in these libraries is accomplished using polymer bound reaction schemes generally described as follows:

A) A polymer bearing a carboxylic acid functionality is coupled with the protected indane of the following formula:

-14-



B) The reactants of step (A) are coupled;

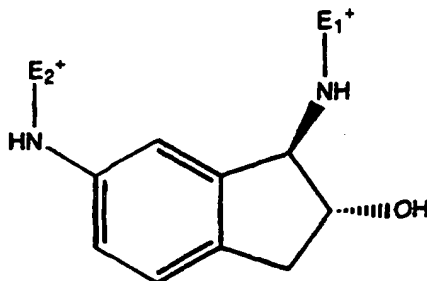
C) The product of step (B) is deprotected resulting in an amine functional indane bound to a resin support;

5 D) The product of step (C) is acylated to attach a first diverse group, E_1^+ ;

E) The product of step (D) is reduced to give the corresponding aniline;

10 F) The product of step (E) is again acylated to attach a second diverse group, E_2^+ ;

G) Cleavage with a base of the product of step (E) from the polymer results in the formation of the product characterized by the formula:



15

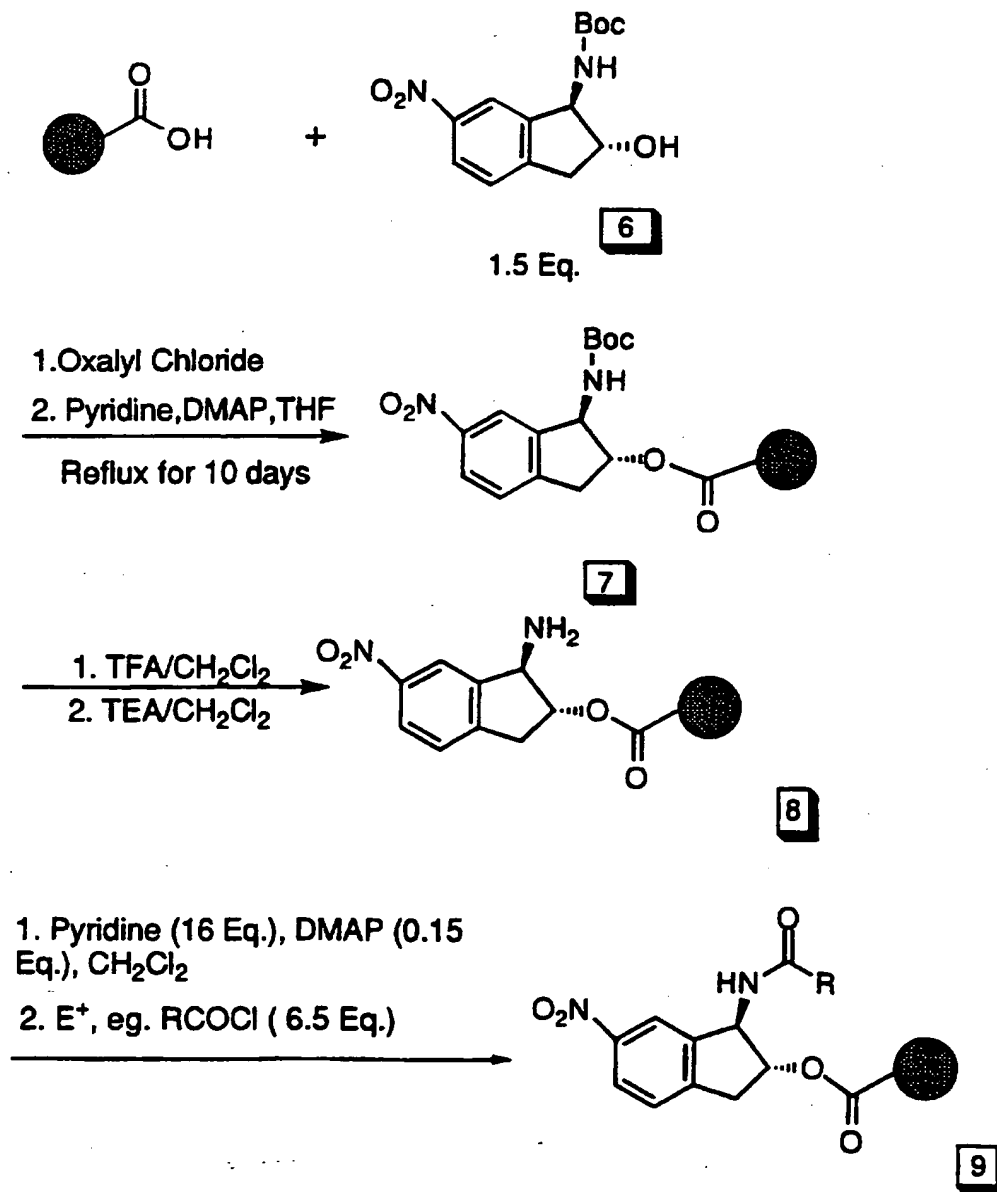
where E_1^+ and E_2^+ are any electrophile.

INDANE LIBRARY AND COMPOUND FORMING PROCESS DESCRIPTION

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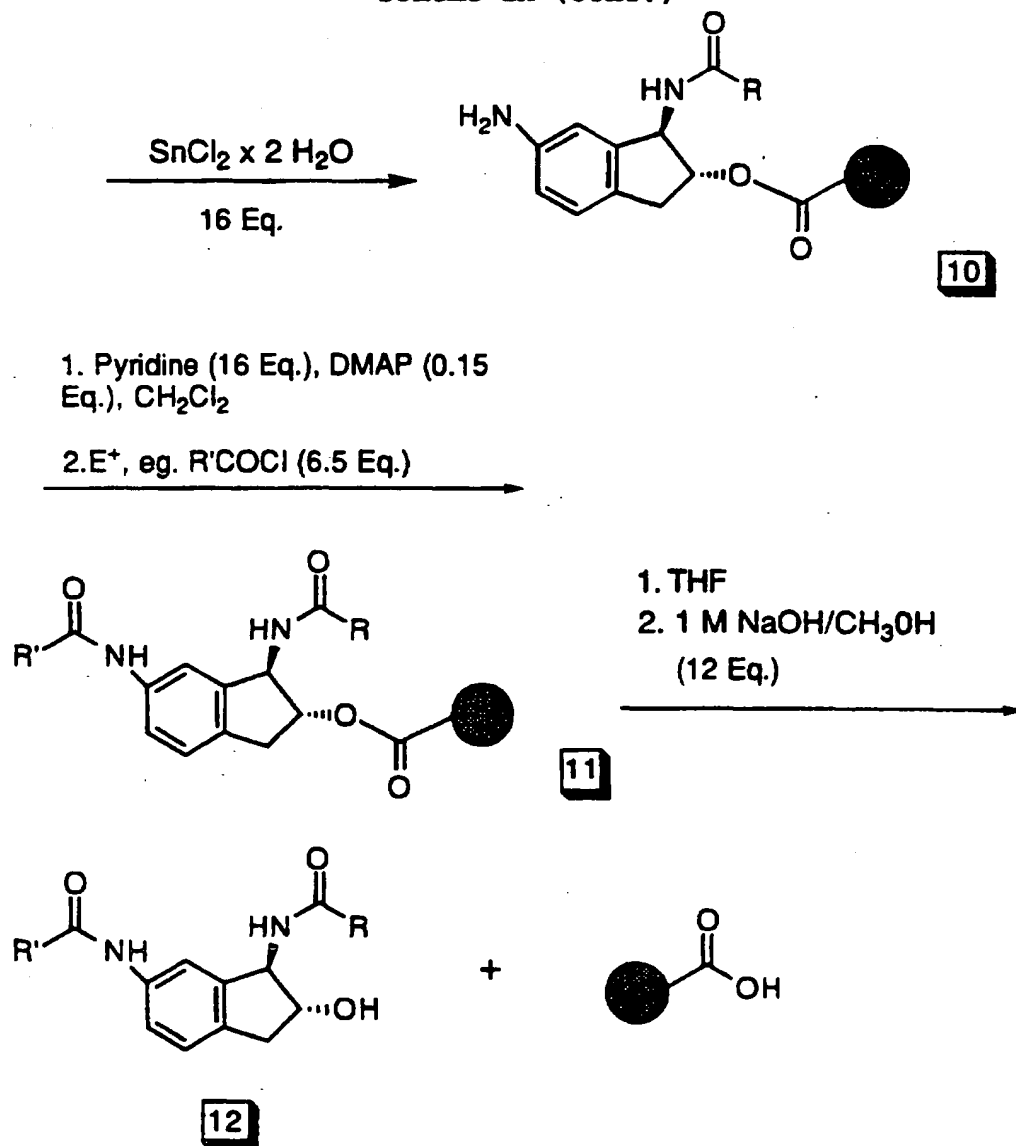
The process steps, more fully described below in the Preparation Section, are illustrated by the following reaction Scheme 1A:

Scheme 1A
SOLID PHASE INDAN CHEMISTRY



-16-

Scheme IA (cont.)



5

Multiple simultaneous synthesis may be performed by a variety of apparatus, such as that shown for multiple simultaneous synthesis U.S. Patent No. 5,324,483; the disclosure of which is incorporated herein by reference.

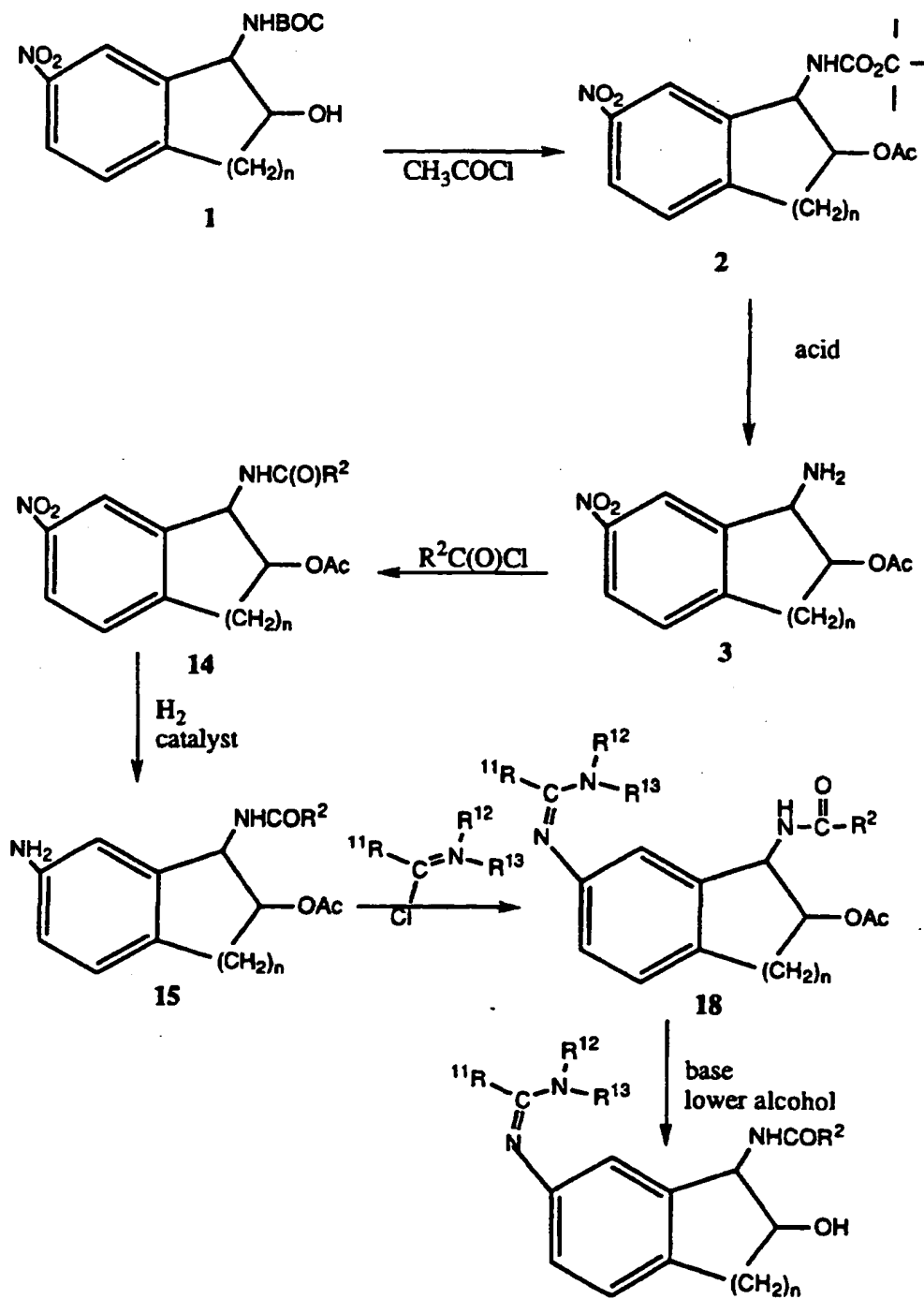
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The compounds of this invention can be prepared using the following general techniques. The skilled artisan

will appreciate that there are alternative methods to obtain the desired compounds claimed herein.

Scheme I

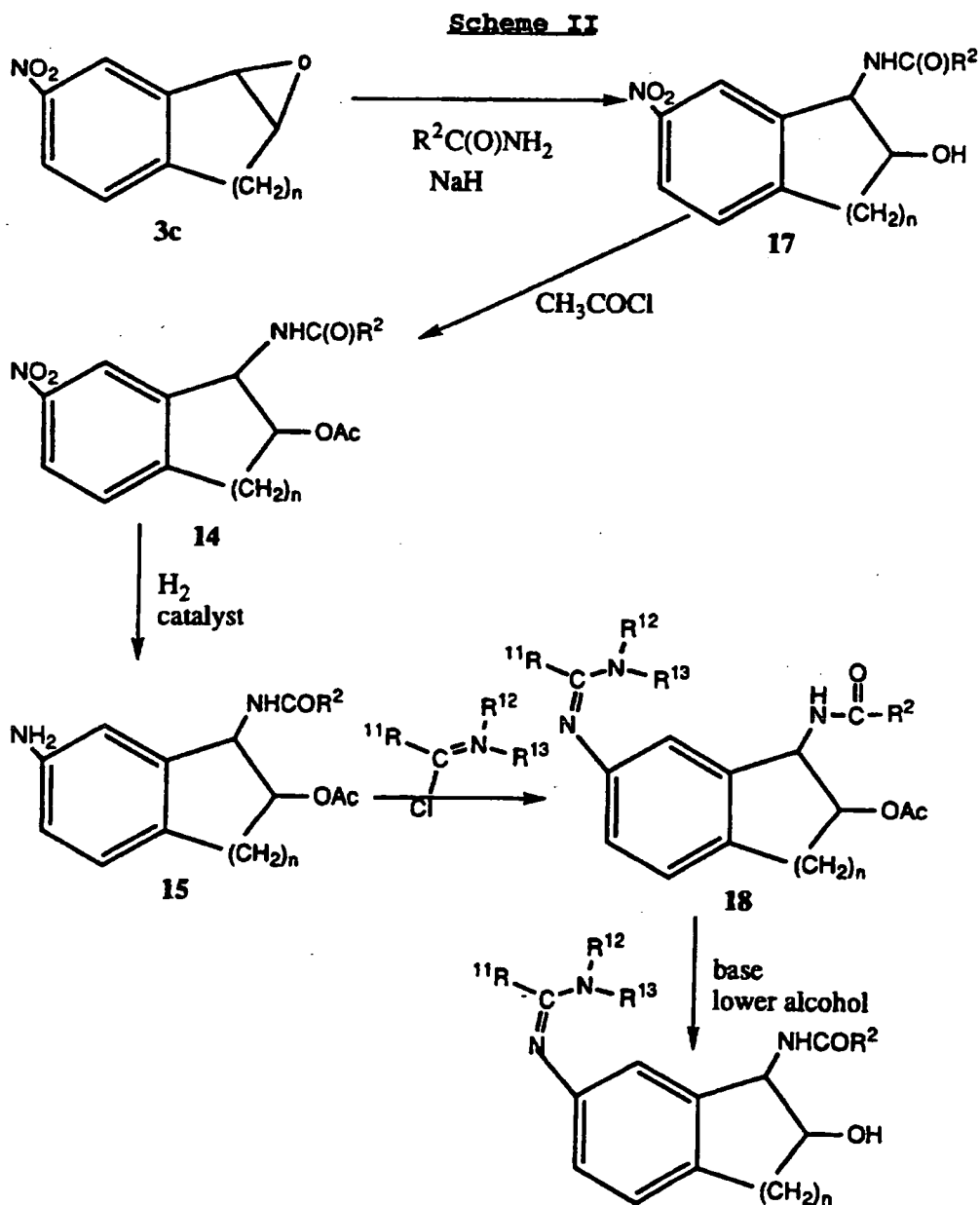
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As illustrated by Scheme I, 1 which is commercially available or may be prepared by the skilled artisan using known methods, is dissolved in a mixture of pyridine, 4-dimethylaminopyridine and an inert organic solvent, wherein preferred inert organic solvents include but are not limited to solvents such as THF or CH_2Cl_2 , as acetyl chloride is added. The mixture may be treated with cold water and the organic layer separated. The organic solution is washed, the organic layer dried, and the solvent evaporated to give 2. A solution of 2 in THF or another appropriate solvent is treated with a stream of dry HCl. The solution is treated with most preferably cold saturated sodium bicarbonate, the organic phase was washed, dried and the solvent evaporated to give 3. A solution of 3 in a mixture of pyridine, 4-dimethylaminopyridine, and CH_2Cl_2 is treated with a solution of an arylsulfonyl chloride and the reaction stirred. The reaction is most preferably poured into ice-water, the organic layer separated and consecutively washed. Preferred washes are with 1 N HCl and brine. The organics are dried and the solvent evaporated to give 14. A solution of 14 is treated with $\text{SnCl}_2 \cdot 2 \text{H}_2\text{O}$. The reaction mixture is preferably poured into ice-water, the reaction made basic, and the mixture extracted. The organic extracts are washed, the solution dried, and the solvent evaporated 15. Alternatively, a solution of 14 in EtOAc or THF is treated with H_2 (about 60 psi) in the presence of a catalyst. Preferred catalysts are chosen from but not limited to the group consisting of PtO_2 , Rainey-Ni, and Pd-C. The catalyst is removed and the solvent evaporated to give 15. A solution of 15 is treated with a solution of a chloroalkylene dialkylammonium chloride. It is noted here that the artisan should recognize that other reagents analogous to chloroalkylidene dialkylammonium chloride can also provide the desired compounds. The reaction was preferably poured into ice-water, the organic layer separated and consecutively washed. Preferred washes are with saturated sodium bicarbonate and brine. The organics are dried and the

solvent evaporated to give **18**. A solution of **18** in base is stirred. The reaction mixture is preferably poured into ice-water and extracted. The organic extracts are washed, dried, and the solvent evaporated to give the desired compound of this invention.

5

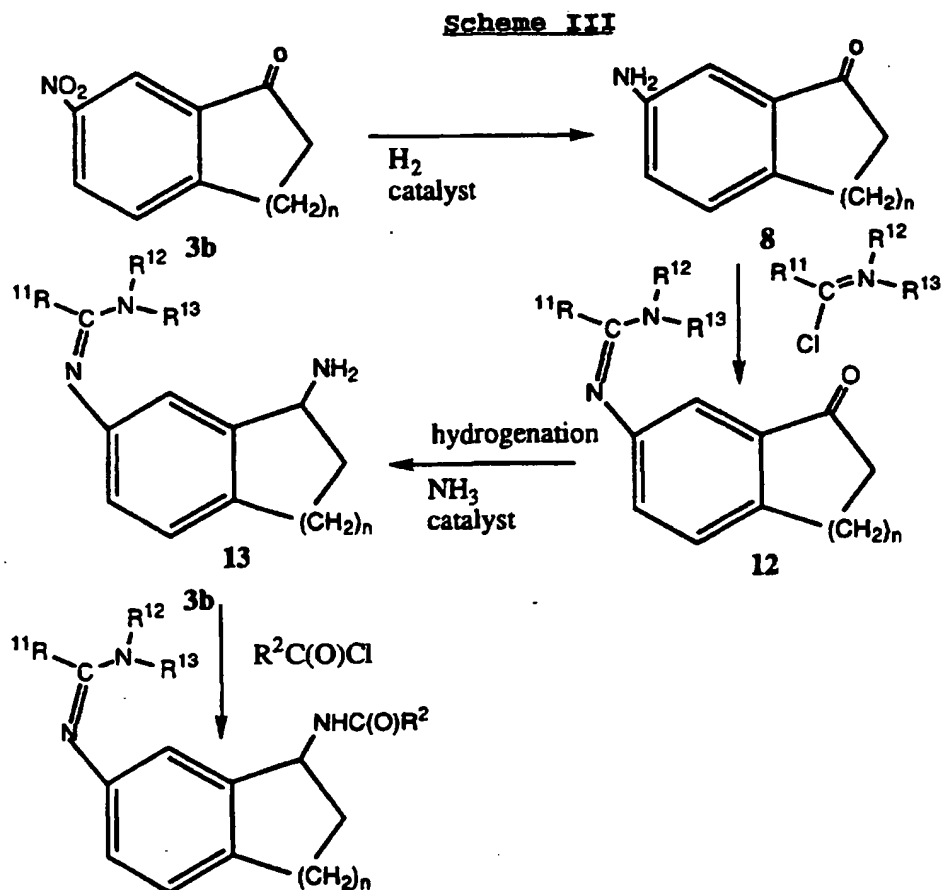


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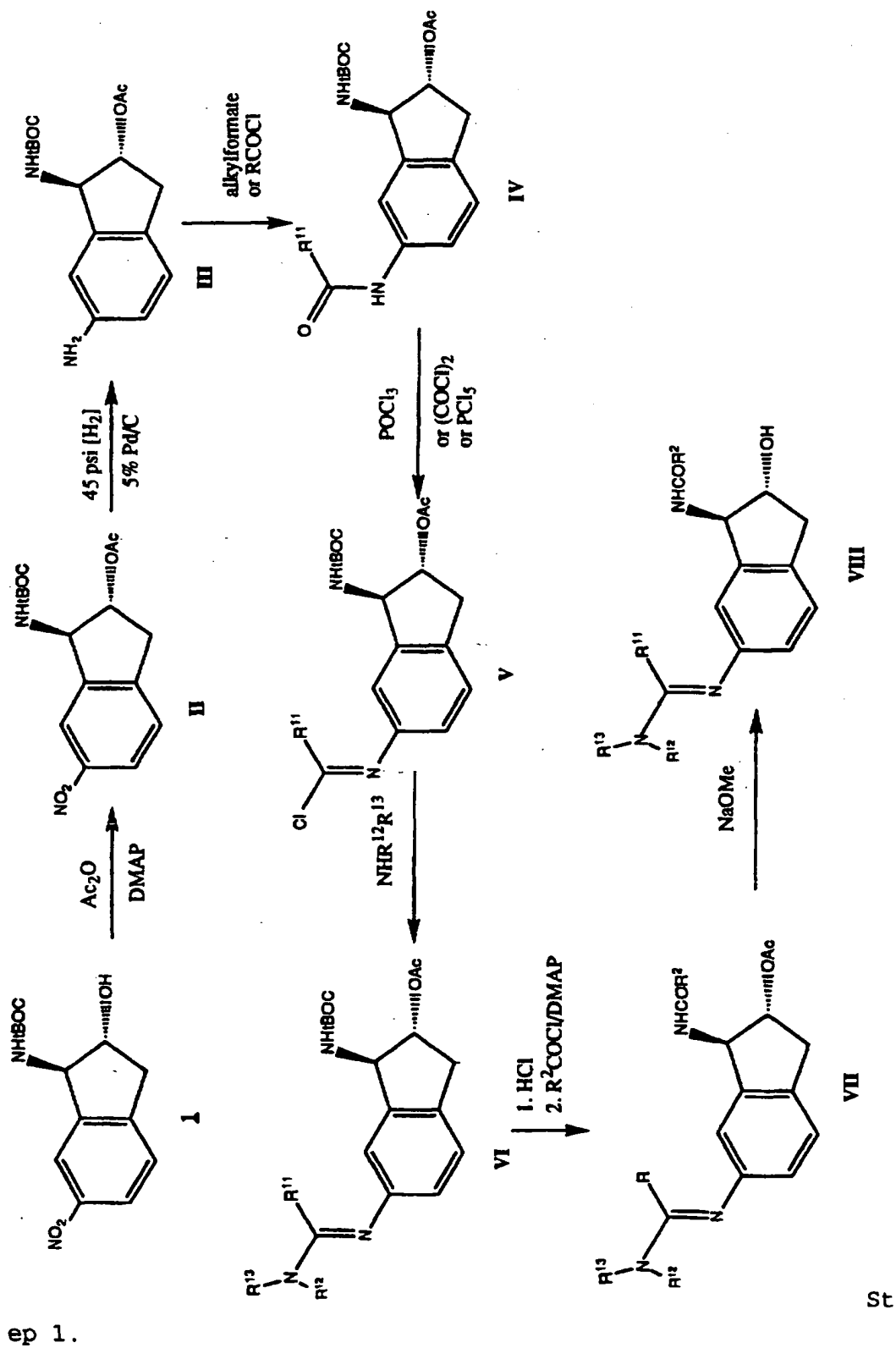
As illustrated by Scheme II, compounds of this invention can be prepared by a solution of a benzamide being

treated with NaH and preferably, the reaction mixture is
 stirred until gas evolution ceased. 1,2-Epoxy-6-nitroindane
 is added. Preferably the 1,2-epoxy-6-nitroindane is added
 at about 60 C and stirred. The reaction is preferably
 5 poured into ice-water and extracted. The organic extracts are
 washed, dried, and the solvent evaporated. The residue is
 chromatographed to obtain **17**. A solution of **17** in a mixture
 of pyridine, 4-dimethylaminopyridine and an inert organic
 solvent, for example but not limited to solvents such as THF
 10 or CH₂Cl₂, as acetyl chloride is added. The reaction is
 preferably treated with cold water and the organic layer
 separated. The organic solution is washed, dried, and the
 solvent evaporated to give **14**. Processing of **14** as in Scheme
 I provides the desired compounds of this invention.

15



As illustrated by Scheme III, certain compounds of this invention can be prepared by a mixture of 6-nitroindan-1-one and a catalyst, which is preferred, but not limited to one chosen from PtO_2 , Rainey-Ni, and Pd-C in EtOH, is treated with hydrogen. The catalyst is removed and the solvent evaporated to give 8. A solution of 8 in a mixture of pyridine, 4-dimethylaminopyridine, and CH_2Cl_2 is treated with a solution of a chloroalkylidene dialkylammonium chloride and the reaction mixture is preferred stirred. It is noted here that the artisan should recognize that other reagents analagous to chloroalkylidene dialkylammonium chloride can also provide the desired compounds. The reaction is preferred poured into ice-water, the organic layer separated and consecutively washed. Preferred washes are with saturated sodium bicarbonate and brine. The organics are dried and the solvent evaporated to give 12. A solution of 12 in a mixture of lower alcohol and NH_3 is treated with hydrogen in the presence of a catalyst which is most preferred, but not limited to, either Pd-C-sulfided or Pt-C sulfided. The catalyst is removed and the solvent evaporated to give 13. A solution of 13 in a mixture of pyridine, 4-dimethylaminopyridine, and CH_2Cl_2 is treated with a solution of an arylsulfonyl chloride. The reaction is preferred poured into ice-water, the organic layer separated and consecutively washed. Preferred washes are with saturated sodium bicarbonate and brine. The organics are dried and the solvent evaporated to give the desired compound of this invention.



Protection of the 3-amino group of compound 5, preferably as a carbamate such as t-butyl carbamate, under standard conditions¹ provided compound 1 (also referred to as 6 supra.). Other similar protecting groups can be utilized in place of t-butyl carbamate. Carbamates are particularly preferred protecting groups for the synthesis described by Step 1.

Step 2.

Reduction of the nitro group may be accomplished using reagents such as SnCl₂, NaBH₄, or more preferably using metal-catalyzed hydrogenation.² Most preferably, Pd/C was used in EtOH at 50 psi and ambient temperature.

Step 3.

The amidine functionality of compounds 57-76 may be prepared from the amine by a variety of methods using reagents such as Gold's reagent. Most preferably the dimethyl amidine was prepared using N,N-dimethylformamide dimethyl acetal under standard conditions.³

Step 4.

The amidine may be exchanged in the presence of higher boiling amines such as pyrrolidine, piperidine, morpholine, or benzyl amine to provide compounds 6-56 and 77-105.⁴

Step 5.

The t-butyl carbamate protecting group was removed under standard conditions (ref 1) using cold trifluoroacetic acid.

¹ Greene and Wuts, Protecting Groups in Organic Chemistry,

² Rylander, Hydrogenation

³ Patel amidine series and Meyers paper and ref. 4.

⁴ Transamidination reaction references.

Step 6.

The trifluoroacetate salt of the amine was reacted with a variety of acid chlorides in the presence of a base such as triethylamine at -10 °C to ambient temperature in a solvent such as methylene chloride to provide compounds VII.

Step 7.

The alcohol group of compounds 5-105 may be acylated or alkylated with reagents such as acetic anhydride in the presence of a base such as triethylamine.

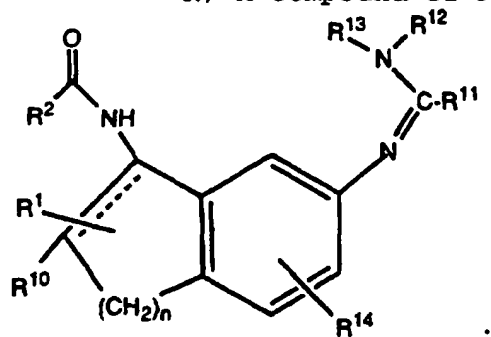
The compounds of this invention can form acid addition salts with a wide variety of inorganic and organic acids. Typical acids which can be used include sulfuric, hydrochloric, hydrobromic, phosphoric, hypophosphoric, hydroiodic, sulfamic, citric, acetic, maleic, malic, succinic, tartaric, cinnamic, benzoic, ascorbic, mandelic, p-toluenesulfonic, benzenesulfonic, methanesulfonic, trifluoroacetic, hippuric and the like. The pharmaceutically acceptable acid addition salts of the compounds of this invention are especially preferred.

The compounds of the present invention are useful for modulating or blocking the M-1 receptor and can be useful for modulating or blocking a serotonin receptor. Certain of the present compounds are preferred for that use. Preferred compounds and embodiments of this invention are those having the following characteristics. The following preferred characteristics may be independently combined to provide further preferred embodiments of this invention:

- A) R^3 is aryl;
- B) R^1 is hydrogen;
- C) R^1 is -OH;
- D) R^3 is substituted phenyl having 3,4-dichloro substituents;
- E) R^2 is substituted phenyl having 3,4-dichloro or meta trifluoromethyl substituents;

-25-

- F) n is one;
 G) the indane ring is saturated;
 H) R³ is bicycloaryl;
 I) R³ is substituted phenyl having a meta NO₂
 5 substituent;
 J) R³ is C₁-C₄ alkyl;
 K) R³ is substituted C₁-C₆ alkyl wherein the
 terminal carbon of the alkyl chain is
 substituted with CO₂R⁴ wherein R⁴ is hydrogen,
 10 methyl, or ethyl;
 L) R¹ is OH, n is 1 and the OH group is located
 at the 2 position of the ring;
 M) a compound of this invention is used for
 treating psychosis;
 15 N) A compound of Formula I:



- O) n is 1;
 P) R² is substituted phenyl;
 Q) A compound of Formula III;
 20 R) A compound of Formula IV, wherein R²⁰ is a
 carbamate;
 S) A compound of Formula I wherein R¹² and R¹³ are
 independently C₁-C₃ alkyl;
 T) A compound of Formula I wherein R¹⁰ is hydrogen
 25 and R¹ is OH;
 U) A compound of Formula I for treating a condition
 associated with modulation of an M4 muscarinic subtype
 receptor;
 V) A compound of Formula I which acts as a
 30 muscarinic receptor agonist.

Further, the present invention contemplates both the cis and trans stereoisomers of the compounds of Formula I. The trans configuration is preferred.

5 The present invention contemplates racemic mixtures as well as the substantially pure enantiomers of the compounds of Formula I. The term "enantiomer" is used herein as commonly used in organic chemistry to denote a compound which rotates the plane of polarization. Thus, the "-
10 enantiomer" rotates the plane of polarized light to the left, and contemplates the levorotary compound of Formula I. The + and - enantiomers can be isolated using classical resolution techniques. One particularly useful reference which describes such methods is JACQUES et. al. ENANTIOMERS, RACEMATES,
15 AND RESOLUTIONS (John Wiley and Sons 1981). Appropriate resolution methods include direct crystallization, entrainment, and crystallization by optically active solvents. Chrisey, L.A. Heterocycles, 267, 30 (1990). A preferred resolution method is crystallization by an optically active acid or by chiral synthesis using the method
20 of A.I. Meyers. Loewe, M.F. et al., Tetrahedron Letters, 3291, 26 (1985), Meyers, A.I. et al., J. Am. Chem. Soc., 4778, 110 (1988). Preferred optically active acids include camphorsulfonic and derivatives of tartaric acid.

25 The compounds of the present invention are known to form hydrates and solvates with appropriate solvents. Preferred solvents for the preparation of solvate forms include water, alcohols, tetrahydrofuran, DMF, and DMSO. Preferred alcohols are methanol and ethanol. Other appropriate solvents may be selected based on the size of the
30 solvent molecule. Small solvent molecules are preferred to facilitate the corresponding solvate formation. The solvate or hydrate is typically formed in the course of recrystallization or in the course of salt formation. One useful reference concerning solvates is Sykes, Peter, A
35 Guidebook to Mechanism in Organic Chemistry, 56+, 6th Ed (1986, John Wiley & Sons, New York). As used herein, the

term "solvate" includes hydrate forms, such as monohydrates and dihydrates.

5 The column chromatography procedures used standard flash chromatography techniques. One well-known reference describing appropriate flash chromatography techniques is Still, W.C. Kahn, and Mitra, *J. Org. Chem.* 1978, 43, 2932. Fractions containing product were generally evaporated under reduced vacuum to provide the product.

10 Optical rotations were obtained using methanol, pyridine, or other suitable solvent.

The hydrochloride salt of the particular compound was prepared by placing the free base into diethyl ether. While stirring this ether solution, a solution of HCl in diethyl ether was added dropwise until the solution became
15 acidic. Alternatively, the ether solution was treated with dry HCl gas.

The maleate salt of the particular compound was prepared by placing the free base in ethyl acetate and treating with maleic acid. The precipitate formed was
20 filtered and dried to provide the corresponding maleate salt of the free base.

I. Muscarinic Activity.

As used herein the term "malfunctioning of the muscarinic cholinergic system" shall have the meaning
25 accepted by the skilled artisan. For example the term shall refer to, but is not in any way limited to, conditions such as glaucoma, psychosis, schizophrenia or schizophreniform conditions, depression, sleeping disorders, epilepsy, and gastrointestinal motility
30 disorders. Other such conditions include Alzheimer's Disease and incontinence.

The pharmacological properties of the compounds of the invention can be illustrated by determining their capability to inhibit the specific binding of ^3H -
35 Oxotremorine-M (^3H -Oxo). Birdsall N.J.M., Hulme E.C., and Burgen A.S.V. (1980). "The Character of Muscarinic

Receptors in Different Regions of the Rat Brain". Proc. Roy. Soc. London (Series B) 207,1.

5 ³H-Oxo labels muscarinic receptor in the CNS
(with a preference for agonist domains of the receptors).
Three different sites are labeled by ³H-Oxo. These sites
have affinity of 1.8, 20 and 3000 nM, respectively. Using
the present experimental conditions only the high and
medium affinity sites are determined.

10

The inhibitory effects of compounds on ³H-oxo
binding reflects the affinity for muscarinic acetylcholine
receptors.

15

All preparations are performed at 0-4°C unless
otherwise indicated. Fresh cortex (0.1-1 g) from male
Wistar rats (150-250 g) is homogenized for 5-10 s in 10 mL
20 mM Hepes pH: 7.4, with an Ultra-Turrax homogenizer. The
homogenizer is rinsed with 10 mL of buffer and the combined
20 suspension centrifuged for 15 min. at 40,000 x g. The
pellet is washed three times with buffer. In each step the
pellet is homogenized as before in 2 x 10 mL of buffer and
centrifuged for 10 min. at 40,000 x g.

25

The final pellet is homogenized in 20 mM Hepes
pH: 7.4 (100 mL per g of original tissue) and used for
binding assay. Aliquots of 0.5 mL is added 25 µL of test
solution and 25 µL of ³H-Oxotremorine (1.0 nM, final
concentration) mixed and incubated for 30 min. at 25°C.

30

Non-specific binding is determined in triplicate using
arecoline (1 µg/mL, final concentration) as the test
substance. After incubation samples are added 5 mL of ice-
cold buffer and poured directly onto Whatman GF/C glass
fiber filters under suction and immediately washed 2 times
35 with 5 mL of ice-cold buffer. The amount of radioactivity
on the filters are determined by conventional liquid

scintillation counting. Specific binding is total binding minus non specific binding.

5 Test substances are dissolved in 10 mL water (if necessary heated on a steam-bath for less than 5 min.) at a concentration of 2.2 mg/mL. 25-75% inhibition of specific binding must be obtained before calculation of IC_{50} . The test value will be given as IC_{50} (the concentration (nM) of the test substance which inhibits the specific binding of 3H -oxo by 50%).

10 $IC_{50} = (\text{applied test substance concentration}) \times (C_x / C_o - C_x) nM$ where C_o is specific binding in control assays and C_x is the specific binding in the test assay. (The calculations assume normal mass-action kinetics).

15 Furthermore the pharmacological properties of the compounds of the invention can also be illustrated by determining their capability to inhibit 3HPRZ (pirenzepine, [N-methyl- 3H]) binding to rat cerebral cortex membranes.

20 Pirenzepine binds selectively to subtype of muscarinic receptors. Historically the type is named the M_1 -site, whereas pirenzepine sensitive site would be more appropriate. Although selective for M_1 -sites pirenzepine also interact with M_2 -sites.

25 All preparations are performed at 0-4°C unless otherwise indicated. Fresh cortex (0.1-1 g) from male Wistar rats (150-200 g) is homogenized for 5-10 s in 10 mL 30 20 mM Hepes pH: 7.4, with an Ultra-Turrax homogenizer. The homogenizer is rinsed with 2 x 10 mL of buffer and the combined suspension centrifuged for 15 min. at 40,000 x g. The pellet is washed three times with buffer. In each step the pellet is homogenized as before in 3 x 10 mL of buffer 35 and centrifuged for 10 min. at 40,000 x g.

The final pellet is homogenized in 20 mM Hepes pH: 7.4 (100 mL per g of original tissue) and used for binding assay. Aliquots of 0.5 mL is added 20 μ L of test solution and 25 μ L of 3 HPRZ (1.0 nM, final conc.), mixed and incubated for 60 min. at 20°C. Non-specific binding is determined in triplicate using atropine (1.0 μ g/mL, final conc.) as the test substance. After incubation samples are added 5 mL of ice-cold buffer and poured directly onto Whatman GF/C glass fiber filters under suction and immediately washed 2 times with 5 mL of ice-cold buffer. The amount of radioactivity on the filters are determined by conventional liquid scintillation counting. Specific binding is total binding minus non-specific binding.

Test substances are dissolved in 10 mL water, at a concentration of 0.22 mg/mL. 25-75% inhibition of specific binding must be obtained before calculation of IC_{50} .

The test value will be given as IC_{50} (the concentration (nM) of the test substance which inhibits the specific binding of 3 HPRZ by 50%).
 $IC_{50} = (\text{applied test substance concentration}) \times (C_x / C_o - C_x) \text{ nM}$
where C_o is specific binding in control assays and C_x is the specific binding in the test assay. (The calculations assume normal mass-action kinetics).

Compounds of this invention showed particularly desirable activity using the muscarinic receptor assays. Most compounds were effective at an IC_{50} concentration of less than 10 μ Molar (no atropine). The muscarinic effect was confirmed by determining if the effect was blocked by atropine.

-31-

II. M4 muscarinic receptor binding assay:

Cyclic AMP Accumulation in Pertussis Toxin-Treated CHO m4 Cells.

5 CHO K1 cells transfected with human m4 receptors
were grown to near confluency in T-150 flasks using
Dulbecco's Modified Eagle Medium (DMEM) containing 10% fetal
bovine serum. Cells were detached with 0.05% trypsin, 0.53 mM
EDTA, and were suspended in medium containing 100 ng/ml
10 pertussis toxin. Cells were plated at 30,000 cells per well
into 96 well plates. Eighteen to twenty hours later the
medium was removed and the cells were washed with serum-free
medium. Attached cells were incubated at 37°C for one hour
after addition of 100 ml of serum free DMEM containing 1 mM
3-isobutyl-1-methylxanthine and 1 mM forskolin plus or minus
15 drugs being tested. Incubations were terminated with 200 ml
per well of serum free DMEM containing 0.3% triton-X-100.
After stopping incubations the plates were allowed to sit for
20 minutes to extract cAMP and samples were then diluted 2.5-
fold and were assayed using the scintillation proximity assay
20 of Amersham (Arlington Heights, IL).

Representative results from the M4 assay are as
follows:

25 Stimulation of cyclic AMP production in CHO-m4 cells.

<u>Compound Number</u>		<u>% Maximum Stimulation</u> <u>Compared to Oxotremorine-M</u>
30	11	34
	12	26
	13	<20
	14	100
	15	76
35	17	56
	18	61
	19	<20
	20	69
	21	23
40	22	<20
	23	<20
	24	22
	25	43

-32-

	26	<20
	27	<20
	28	<20
	29	<20
5	30	<20
	31	45
	32	<20
	33	45
	34	45
10	35	65
	36	<20
	37	76
	38	<20
	39	43
15	40	96
	41	<20
	44	41
	45	<20
	46	154
20	47	<20
	57	5
	58	74
	59	22
	60	100
25	61	39
	62	27
	63	13
	64	52
	65	30
30	66	0
	67	7
	68	0
	69	14
	70	18
35	71	95
	72	4
	73	11
	74	8
	75	6
40	76	130
	77	214
	88	52
	97	36
	98	73
45		

III. Psychosis Studies.

The antipsychotic activity of the presently claimed compounds can be demonstrated in models using well-established procedures. For example the compounds are studied to determine if they antagonize apomorphine-induced

climbing behavioral and hypothermia in mice (Moore, N.A. et al. *Psychopharmacology* 94 (2), 263-266 (1988), and 96, 539 (1988)) which measures the ability of the compound to prevent the disruption of climbing response produced by 24 hour pre-treatment with N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ), a dopamine receptor inactivating agent (Meller et al. *Central D1 dopamine receptors*, Plenum Press, 1988).and/or inhibit a conditioned avoidance response in rats (ED₅₀ 4-7 mg/kg).

The conflict procedure used is based on the method of Geller and Seifter, *Psychopharmacologia* 1: 482-492, (1960). Rats are trained on a multiple schedule consisting of three components. Individual components are as follows: 1) for 9 minutes, lever pressing was reinforced on a variable interval 30 second schedule (VI 30, reward). This period is signaled by illumination of the houselight alone. 2) During the following 3-minute period, lever presses are recorded but had no programmed consequence (time-out). 3) Lever pressing is reinforced according to a fixed ratio 10 second food presentation (FR10) for 3 minutes; however, each reinforced response is accompanied by an electric current (0.5 mA) being applied to the grid floor for 500 msec (conflict). This component is signaled by illumination of the houselight and three cue lights on the front panel. This sequence of three components (reward/time-out/conflict) are presented twice in the same order during the daily 30 minute session. Animals are given extensive training on this schedule until the following criteria had been satisfied: 1) rates of responding during the individual VI30 components do not differ by more than 10%; 2) rates of responding during time-out and conflict are less than 10% of the rate during the VI component; and 3) the above criteria are satisfied for a period of five days.

After the training procedure, drug testing is initiated. During this period, the animals are dosed orally with either test compounds or vehicle in a

randomized order 60 minutes before testing. At least two drug-free training days occur between test sessions. This test indicates that the compound has anxiolytic properties which are not observed with typical antipsychotic agents.

5 Spealman et al., J. Pharmacol. Exp. Ther., 212:435-440, 1980.

Further, the pharmacological profile of the claimed compounds is desirable for use in the treatment of other conditions which are related to the mediation of a muscarinic receptor. Such conditions include for example, Alzheimer's Disease, glaucoma, irritable bowel syndrome, bladder dysfunction and incontinence, treatment of pain, analgesia, Huntington's Disease, epilepsy, Parkinson's Disease, anxiety, and other psychotic conditions as described in the DSM-IV.

10

15 While it is possible to administer a compound of the invention directly without any formulation, the compounds are preferably employed in the form of a pharmaceutical formulation comprising a pharmaceutically acceptable excipient and at least one compound of the invention. Such compositions contain from about 0.1 percent by weight to about 90.0 percent by weight of a present compound. As such, the present invention also provides pharmaceutical formulations comprising a compound of the invention and a pharmaceutically acceptable excipient therefor.

20

25 In making the compositions of the present invention, the active ingredient is usually mixed with an excipient which can be a carrier, or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container.

30 When the carrier serves as a diluent, it can be a solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active ingredient. Thus, the composition can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, emulsions, solutions, syrups, suspensions, aerosols (as a solid or in a liquid medium), and soft and hard gelatin capsules.

35

The compounds of the invention may be delivered transdermally, if desired. Transdermal permeation enhancers and delivery systems, including patches and the like, are well known to the skilled artisan.

5 Examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum acacia, calcium phosphate, alginates, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, tragacanth, gelatin, syrup,
10 methyl cellulose, methyl- and propylhydroxy- benzoates, talc, magnesium stearate, water, and mineral oil. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavoring agents. The formulations of the invention may be formulated
15 so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

 The compounds of this invention may be delivered transdermally using known transdermal delivery systems and
20 excipients. Most preferably, a compound of this invention is admixed with permeation enhancers including, but not limited to, propylene glycol, polyethylene glycol monolaurate, and azacycloalkan-2-ones, and incorporated into a patch or similar delivery system. Additional excipients
25 including gelling agents, emulsifiers, and buffers may be added to the transdermal formulation as desired.

 For oral administration, a compound of this invention ideally can be admixed with carriers and diluents and molded into tablets or enclosed in gelatin capsules.

30 The compositions are preferably formulated in a unit dosage form, each dosage containing from about 0.1 to about 500 mg or more, usually about 5 to about 300 mg, of the active ingredient. The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for
35 human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to

produce the desired therapeutic effect in association with a suitable pharmaceutical carrier.

In order to more fully illustrate the operation of this invention, the following formulation examples are provided. The examples are illustrative only, and are not intended to limit the scope of the invention. The formulations may employ as active compounds any of the compounds of the present invention.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	<u>Amount Per Capsule</u>	<u>Concentration by Weight (percent)</u>
A compound of this invention	250 mg	55.0
starch dried	200 mg	43.0
magnesium stearate	<u>10 mg</u>	<u>2.0</u>
	460 mg	100.0

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

Formulation 2

5

Capsules each containing 20 mg of medicament are made as follows:

10		<u>Amount Per Capsule</u>	<u>Concentration by Weight (percent)</u>
	A compound of this	20 mg	10.0
15	invention		
	starch	89 mg	44.5
	microcrystalline		
	cellulose	89 mg	44.5
20	magnesium stearate	<u>2 mg</u>	<u>1.0</u>
		200 mg	100.0 mg

25

The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve and filled into a hard gelatin capsule.

Formulation 3

5

Capsules each containing 100 mg of medicament are made as follows:

10		Amount Per <u>Capsule</u>	Concentration by Weight <u>(percent)</u>
	a compound of this invention	100 mg	30.00
15	polyoxyethylene sorbitan monooleate	50 mg	0.02
	starch powder	<u>250 mg</u>	<u>69.98</u>
20		350.05 mg	100.00

The above ingredients are thoroughly mixed and placed in an empty gelatin capsule.

25

Formulation 4

5 Tablets containing 10 mg of active ingredient are made as follows:

	<u>Amount Per Capsule</u>	<u>Concentration by Weight (percent)</u>
10		
	a compound of this invention	10 mg 10.0
	starch	45 mg 45.0
15		
	microcrystalline cellulose	35 mg 35.0
20		
	polyvinylpyrrolidone (as 10% solution in water)	4 mg 4.0
	sodium carboxymethyl starch	4.5 mg 4.5
25		
	magnesium stearate	0.5 mg 0.5
	talc	<u>1 mg</u> <u>1.0</u>
30		
		100 mg 100.0

35 The active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granule so produced is dried at 50°-60° C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to

40 the granule which, after mixing, is compressed on a tablet machine to yield a tablet weighing 100 mg.

Formulation 5

5 A tablet formulation may be prepared using the ingredients below:

	<u>Amount Per</u> <u>Capsule</u>	<u>Concentration</u> <u>by Weight</u> <u>(percent)</u>
10 A compound of this invention	250 mg	38.0
15 microcrystalline cellulose	400 mg	60.0
silicon dioxide fumed	10 mg	1.5
20 stearic acid	<u>5 mg</u>	<u>0.5</u>
	665 mg	100.0

The components are blended and compressed to form tablets each weighing 665 mg.

Formulation 6

5

Suspensions each containing 5 mg of medicament per 5 ml dose are as follows:

10		per 5 ml of <u>suspension</u>
	A compound of this invention	5 mg
	sodium carboxymethyl cellulose	50 mg
15	syrup	1.25 ml
	benzoic acid solution	0.10 ml
20	flavor	q.v.
	color	q.v.
	water	q.s. to 5 ml

25

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethylcellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color is diluted with some of the water and added to the paste with stirring. Sufficient water is then added to produce the required volume.

30

Formulation 7

An aerosol solution is prepared containing the following components:

5		Concentration by Weight (percent)
10	A compound of this invention	0.25
	ethanol	29.75
15	Propellant 22 (chlorodifluoromethane)	<u>70.00</u>
		100.00

20 The active compound is mixed with ethanol and the mixture added to a portion of the Propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted further with the remaining amount of propellant. The valve units are then fitted to the container.

25 The following Examples further illustrate certain of the compounds of the present invention, and methods for their preparation. The examples are illustrative only, and are not intended to limit the scope of the invention.

30

Preparation 1

Indane compounds are formed on a solid polymer support by the a series of process steps illustrated by the following 12 steps which are presented Preparation 1, Example 1 and Example 2, this process is further illustrated by Scheme IA, *supra*.

35 Steps 1-4 of Synthesis of Scheme IA.

1. To a solution of 1-indanone (25 g, 0.189 mol) in concentrated H₂SO₄ (84 ml) at 0°C was added a solution of

KNO₃ (8.33 g, 0.0824 mol) in H₂SO₄ (40 ml) as to maintain an internal temperature below 15°C. After stirring at 0°C for 1 hr., the reaction mixture was poured into crushed ice and stirred vigorously for 30 min. The suspension was then
5 filtered, air dried, and purified by LC (5% ethyl acetate/toluene) to provide 1^a (18.90 g, 56%) as a pale yellow solid.

2. A solution of 1^a (18.90 g, 0.107 mol) in methanol (300ml) was cooled to 0°C and NaBH₄ (4.04g, 0.107 mol) was added in
10 several small portions. The reaction was then stirred overnight at 25°C. The solution was quenched at 0°C with methanolic HCl (200 ml), concentrated under reduced pressure, redissolved in CH₂Cl₂, washed with H₂O, and the organic layer reconcentrated to provide the crude alcohol as a brown
15 solid.

3. To a solution of crude alcohol in toluene (300 ml) was added a catalytic amount of p-toluenesulfonic acid and the reaction was refluxed for 1 hr. using a Dean Stark trap to remove the H₂O. The organic layer was washed with sat'd.
20 NaHCO₃ (3 x 200 ml), dried over MgSO₄, solvent removed under vacuum, and the product recrystallized from methanol to afford 3^a (13.41g, 78% over two steps) as a tan solid.
4. To a solution of 3^a (10.53g, 0.0653 mol) in dichloromethane (350ml) at 0°C was added mCPBA (29g, 0.0924
25 mol) in small amounts over the course of 1 hr. After stirring overnight at 25°C, the mixture was washed with sat'd Na₂SO₃ (2 x 200 ml), sat'd NaHCO₃ (2 x 200ml), filtered through a cotton plug, and concentrated under vacuum. The product shall be referred to as 4^a.

30

Example 1

Step 5 of Synthesis of Scheme IA.

5. A suspension of 4^a in concentrated NH₄OH (250 ml) was heated overnight in an oil bath at 45°C. The next day H₂O
35 was added and the basic aqueous layer was sat'd. with NaCl. The cloudy reaction mixture was extracted with THF until no more product could be seen by TLC. Organic layers were

combined, dried over MgSO_4 , concentrated, and recrystallized from ethyl acetate to give 5^a (11.54 g, 91% over two steps) as a fluffy tan solid. m.p. 148-150 °C.

5

Example 2

Step 6 of Synthesis of Scheme IA.

To a solution of 5^a (8.34g, 0.0429 mol) in THF (200 ml) was added a solution of di-tert-butylidicarbonate (11.25g, 0.0515 mol) in THF (50 ml). After stirring 1 hr at 25°C, the solvent was removed under reduced pressure and the resulting solid was recrystallized from ethyl acetate to afford 6^a (11.37g, 90%) as a white solid.

Step 7 of synthesis of Scheme IA. Under an N_2 atmosphere a 3 L three-necked round bottomed flask equipped with an overhead stirrer and addition funnel was charged with carboxylated polystyrene resin (70 g, 2.77 mmol $\text{CO}_2\text{H/g}$ resin), anhydrous dichloromethane (1000ml), and anhydrous DMF (10 ml). Next, oxalyl chloride (50.75 ml, 0.582 mol) was added via a slow dropwise addition from an addition funnel. After refluxing overnight under N_2 , the solvent was removed under vacuum using a gas dispersion tube. The resin was subsequently washed with anhydrous dichloromethane (3 x 500 ml). Once the last wash was complete, the resin was dried under vacuum for 2-3 hrs. At this time, the polymer was resuspended in dry THF (1000 ml) followed by the addition of dry pyridine (314 ml, 3.88 mol), DMAP (11.85 g, 0.0970 mol), and 6^a (85.62 g, 0.291 mol). The mixture was refluxed for 10 days under an inert atmosphere. The solvent was removed by vacuum filtration and the resin was washed with THF (3 x 300 ml), CH_2Cl_2 (3 x 300 ml), and dried overnight in a vacuum oven to provide 7^a (122.18 g) as a tan resin.

Example 3

Step 8-12 of total synthesis Scheme IA.

Into a round bottomed flask equipped with a stir bar was placed 7^a (28mg, 0.02827 mmol), 0.500 ml dichloromethane, and TFA (0.109 ml, 0.14135 mmol). The reaction mixture was

stirred at 25°C overnight, resin collected by filtration, resuspended in 10%TEA/CH₂Cl₂, stirred for 15 min., filtered again, and finally washed with dichloromethane to afford 8^a.
9. Into a 10 ml round bottomed flask was placed 7^a (0.02827 mmol) followed by 0.5 ml of a solution of pyridine (0.03659 ml, 0.4524 mmol) and DMAP (0.518 mg, 0.004241 mmol) in dichloromethane. Next, a 1M solution of an electrophile in dichloromethane (0.1838 ml, 0.1838 mmol) was added and the resulting mixture was stirred overnight at 25°C. At this time the solvent was removed by vacuum filtration and the resin was washed with CH₂Cl₂, DMF, methanol, DMF, methanol, and CH₂Cl₂. This product is referred to as 9^a.
10. To a solution of 9^a (0.02827 mmol) in DMF (0.625 ml) was added SnCl₂ x 2 H₂O (102 mg, 0.4524 mmol). Upon stirring at 25°C for 48 hrs, the resin was isolated by filtration and washed with CH₂Cl₂, DMF, methanol, DMF, methanol, and CH₂ Cl₂ to give 10^a.
11. Into a 10 ml round bottomed flask was placed 10^a (0.02827 mmol) followed by 0.5 ml of a solution of pyridine (0.03659 ml, 0.4524 mmol) and DMAP (0.518 mg, 0.004241 mmol) in dichloromethane. Next, a 1M solution of an electrophile in dichloromethane (0.1838 ml, 0.1838 mmol) was added and the resulting mixture was stirred overnight at 25°C. At this time the solvent was removed by vacuum filtration and the resin was washed with CH₂Cl₂, DMF, methanol, DMF, methanol, and CH₂Cl₂ to give 11^a.
12. To a flask containing 11^a (0.02827 mmol) was added a 1M solution of NaOH in methanol (0.375 ml, 0.375 mmol) and THF (0.400 ml). After overnight stirring at 25°C, the reaction was neutralized with 4M HCl in methanol (0.100ml, 0.400 mmol), resin filtered, and the filtrate was concentrated under reduced pressure to provide 12^a.

Example 4

A 3 gallon stainless steel hydrogenation reactor was charged with 2.79 g (5% wt. load) of 5% Pd/C under a nitrogen purge. The catalyst was then wetted with toluene

(25 mL). To this mixture was added a solution of **1** (55.39 g (0.188 mol) in 3A-EtOH (6 L). After purging the reactor with nitrogen, the reaction vessel was pressurized to 45 psi with hydrogen and stirred at room temperature for 4.5 h. TLC (Silica, 90/10 CH₂Cl₂/MeOH + 1% NH₄OH) indicated the reaction was complete. The mixture was filtered through Hi-Flo and the filter cake rinsed with CH₂Cl₂ (2 L). The filtrate was transferred to a 12 L Buchii flask and concentrated in vacuo to afford **2** (47.79 g, 96%) as a white solid.

To a solution of **2** (5.0 g, 0.089 mol) in MeOH (50 mL) was added dimethylformamide-dimethylacetal (3.77 mL, 0.028 mol). After stirring at reflux for 1 h, a second aliquot of dimethylformamide-dimethyl acetal (3.77 mL, 0.028 mol) was added and reflux continued for another 1.5 h. TLC (Silica, 90/10 ethyl acetate/hexanes + 2% Et₃N) indicated the reaction was complete. The mixture was cooled to room temperature and concentrated to a thick oil. The crude product was dissolved in CH₂Cl₂ (100 mL), washed with 1 x 25 mL D.I. H₂O, 2 x 50 mL 5% NaHCO₃, and dried over Na₂SO₄. Concentration in vacuo afforded **3** (6.17 g, 96%) as a light tan foam.

A solution of **3** (1.66 g, 0.0049 mol) in neat pyrrolidine (15 mL) was treated with 5 mg of (NH₄)₂SO₄ and heated to 80 °C in an oil bath. After 4 hrs at 80 °C, a small aliquot of the reaction mixture was removed, stripped to dryness and analyzed by NMR (CDCl₃, 500 MHz). Observation of a new amidine-H signal at 7.78 ppm with no signal remaining at 7.52 ppm indicated the reaction was complete. The mixture was concentrated to remove the excess pyrrolidine. The resulting crude oil was dissolved in CH₂Cl₂ (50 mL), washed with 1 x 25 mL H₂O, 1 x 25 mL 5% NaHCO₃, and 1 x 25 mL brine, then dried over Na₂SO₄. Concentration in vacuo afforded **4** as a tan foam (1.70 g, 95%).

Example 5

Compound 4 (1.49 g, 0.0041 mol) was dissolved in cold (-5 °C) trifluoroacetic acid (15 mL) and stirred at -5 °C to -10 °C for 15 minutes. TLC (Silica, 90/10 CH₂Cl₂/MeOH + 1% NH₄OH) indicated the reaction was complete. The mixture was concentrated in vacuo to remove excess trifluoroacetic acid. The crude oil was dissolved in 2B-EtOH (4 mL) and treated with the dropwise addition of diethyl ether (30 mL). The resulting precipitate was filtered, washed with diethyl ether (15 mL) and dried under vacuum at 40 °C. Compound 5 (1.70 g, 87%) was recovered as a white solid.

Examples 6-105

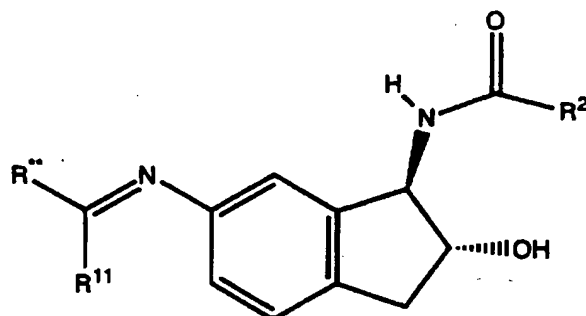
Examples 6 through 105 were prepared using substantially the procedure described as follows, using the corresponding reagents to provide the desired compound:

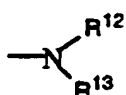
Compound 5 (106 mg, 0.000224 mol) was suspended in CH₂Cl₂ (3.3 mL), cooled to 0 °C and treated with Et₃N (0.09 mL, 0.000894 mol). The resulting solution was treated with benzoyl chloride (31 mL, 0.000268 mol) and the mixture stirred for 0.5 h. With TLC (Silica, 90/10 CH₂Cl₂/MeOH + 1% NH₄OH) showing the reaction to be complete, the mixture was diluted with CH₂Cl₂ (2.5 mL) and quenched with H₂O (2.5 mL). The organic layer was washed with 1 x 5 mL H₂O, 3 x 2.5 mL 5% NaHCO₃, and 1 x 2.5 mL brine. After drying over Na₂SO₄, the mixture was concentrated in vacuo to afford 6 (76 mg, 97%) as a white foam.

Examples 6-105

Examples 6-105 are presented in the following table. The "Comp.#" corresponds to both the compound number and example number.

-48-



R^{**} is ; wherein R², R¹¹, R¹², and R¹³ are defined as described supra.

5

Comp #	R ^{**}	R ¹¹	R ²	Electros pray Ionizati on M.S. (M + 1)
6	1-Pyrrolidine	H	Phenyl	350
7	1-Pyrrolidine	H	3,5 di(trifluoromethy l)-phenyl	486
8	1-Pyrrolidine	H	4-Butoxy-Phenyl	422
9	1-Pyrrolidine	H	Cyclopentyl	342
10	1-Pyrrolidine	H	6-Chloro-3-Pyridinyl	385
11	1-Pyrrolidine	H	Cyclohexyl	356
12	1-Pyrrolidine	H	2-Chloro-3-Pyridinyl	385
13	1-Pyrrolidine	H	4-Cyano-Phenyl	375
14	1-Pyrrolidine	H	3,5 dichlorophenyl	419
15	1-Pyrrolidine	H	1-Napthyl	400
16	1-Pyrrolidine	H	4-Ethylphenyl	378
17	1-Pyrrolidine	H	2-Napthyl	400
18	1-Pyrrolidine	H	4-Trifluoromethyl- Phenyl	418

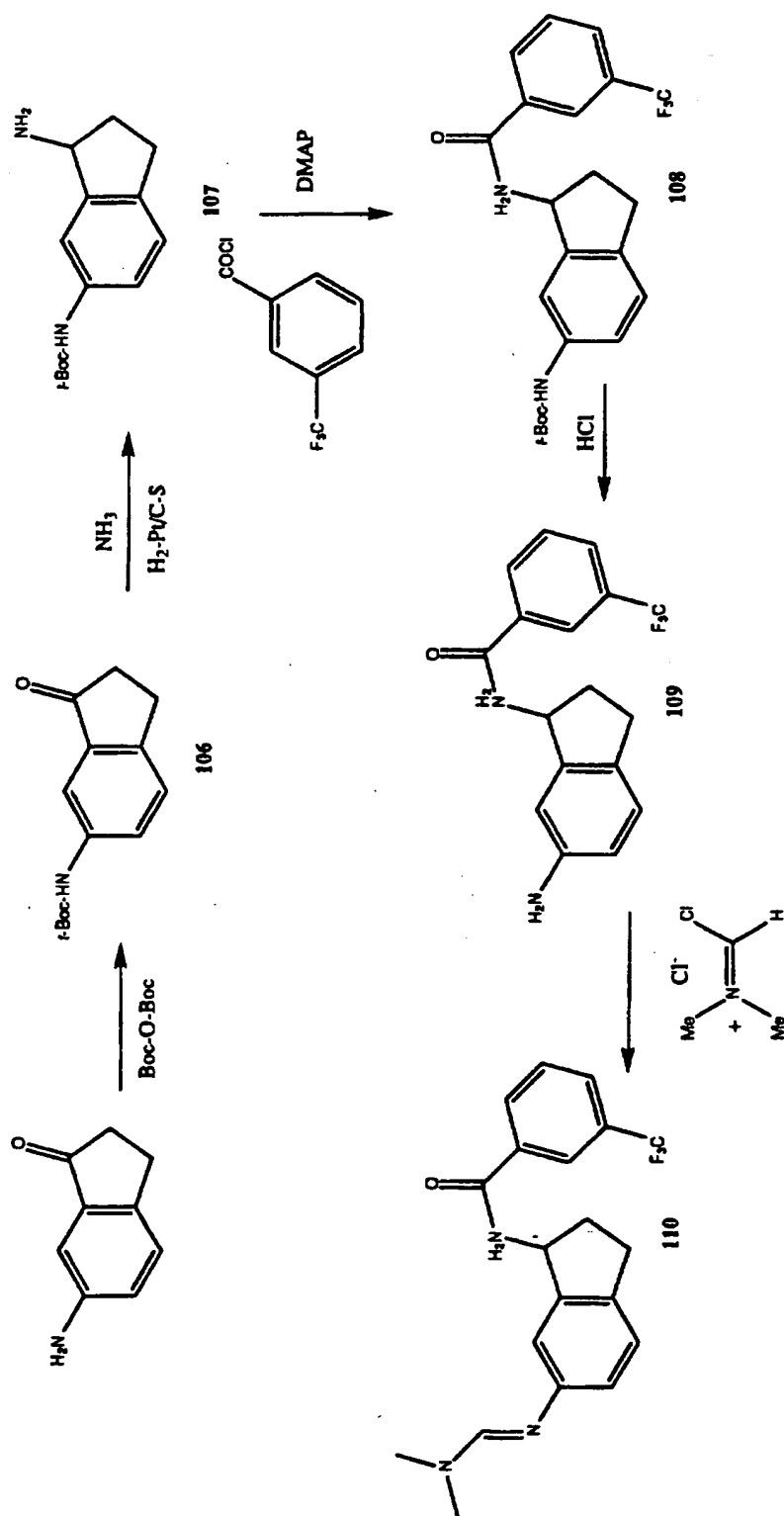
19	1-Pyrrolidine	H	Trifluoromethyl	342
20	1-Pyrrolidine	H	2-Chloro-4-Nitro-Phenyl	429
21	1-Pyrrolidine	H	2-Thiophene	356
22	1-Pyrrolidine	H	4-Tosyl	396
23	1-Pyrrolidine	H	3,5 difluoro Phenyl	386
24	1-pyrrolidine	H	2,3 difluoro-Phenyl	386
25	1-Pyrrolidine	H	3-Nitro-Phenyl	395
26	1-Pyrrolidine	H	4-Propylphenyl	392
27	1-Pyrrolidine	H	2,4,6 Trimethylphenyl	392
28	1-Pyrrolidine	H	Methylenethiophenyl	396
29	1-Pyrrolidine	H	2,3,6 Trifluorophenyl	404
30	1-Pyrrolidine	H	3-Fluorophenyl	368
31	1-Pyrrolidine	H	2,3 Dichlorophenyl	419
32	1-Pyrrolidine	H	2,5 Difluorophenyl	386
33	1-Pyrrolidine	H	2,3,4 Trifluorophenyl	404
34	1-Pyrroldine	H	3-Methoxy-Phenyl	380
35	1-Pyrrolidine	H	2-Trifluoromethyl Phenyl	418
36	1-Pyrrolidine	H	3,5 Dimethoxy-Phenyl	410
37	1-Pyrrolidine	H	3-Tolyl	364
38	1-Pyrrolidine	H	3-Cyano-Phenyl	375
39	1-Pyrrolidine	H	3,4,5 Trifluoro-Phenyl	404
40	1-Pyrrolidine	H	2,3,4,5 Tetrafluoro-Phenyl	422
41	1-Pyrrolidine	H	Cyclobutyl	328
42	1-Pyrrolidine	H	2-Methoxy-Phenyl	380
43	1-Pyrrolidine	H	2-Tolyl	364
44	1-Pyrrolidine	H	2-Chlorophenyl	384

45	1-Pyrrolidine	H	4-Butyl-Phenyl	406
46	1-Pyrrolidine	H	2,6 Dichlorophenyl	419
47	1-Pyrrolidine	H	2,4,6 Trichloro-Phenyl	453
48	1-Pyrrolidine	H	2-Quinoxyl	402
49	1-Pyrrolidine	H	2,4,5 Trifluoro-Phenyl	404
50	1-Pyrrolidine	H	2,6 Difluoro-Phenyl	386
51	1-Pyrrolidine	H	2-Iodophenyl	476
52	1-Pyrrolidine	H	2,4 Difluorophenyl	386
53	1-Pyrrolidine	H	Undecanyl	414
54	1-Pyrrolidine	H	4-Ethoxy-Phenyl	394
55	1-Pyrrolidine	H	4-Trifluormethyl-5-Fluoro-Phenyl	436
56	1-Pyrrolidine	H	2-Trifluoromethyl-6-Fluoro-Phenyl	436
57	Dimethyl-amine	H	Phenyl	324
58	Dimethyl-amine	H	3,5 Dichlorophenyl	393
59	Dimethyl-amine	H	4-Butoxy-Phenyl	396
60	Dimethyl-amine	H	3,5 di-(trifluoromethyl)-Phenyl	460
61	Dimethyl-amine	H	3-Cyano-Phenyl	349
62	Dimethyl-amine	H	Cyclopentyl	316
63	Dimethyl-amine	H	2-Napthyl	374
64	Dimethyl-amine	H	3-Trifluoromethyl-5-Fluoro-Phenyl	410
65	Dimethyl-amine	H	3,4,5 Trifluoro-Phenyl	378
66	Dimethyl-amine	H	Trifluoromethyl	316
67	Dimethyl-amine	H	4-Ethyl-Phenyl	352
68	Dimethyl-amine	H	3-Chloro-2-Thiophene	364

69	Dimethyl-amine	H	2-Benzothiophene	380
70	Dimethyl-amine	H	4-Butyl-Phenyl	380
71	Dimethyl-amine	H	1-Napthyl	374
72	Dimethyl-amine	H	3,4 Dichloro-Benzenesulfonyl	429
73	Dimethyl-amine	H	2-Chloro-3-Pyridinyl	359
74	Dimethyl-amine	H	6-Chloro-3-Pyridinyl	359
75	Dimethyl-amine	H	4-Trifluoromethyl-Phenyl	392
76	Dimethyl-amine	CH ₃	3,4 Dichlorophenyl	407
77	1-Piperidine	H	3,4 Dichlorophenyl	433
78	1-Piperidine	H	3-Trifluoromethoxy-Phenyl	448
79	1-Piperidine	H	3-Fluorophenyl	382
80	1-Piperidine	H	3-Chlorophenyl	398
81	1-Piperidine	H	3-Methoxy-Phenyl	394
82	1-Piperidine	H	3-Trifluoromethyl-Phenyl	432
83	1-Piperidine	H	2-Tolyl	378
84	1-Piperidine	H	2,4 Dichlorophenyl	433
85	1-Piperidine	H	2-Chloro-4-Nitro-Phenyl	444
86	1-Piperidine	H	4-Propyl-Phenyl	406
87	1-Piperidine	H	4-Methoxyphenyl	394
88	1-Piperidine	H	2,3 Dichlorophenyl	433
89	1-Piperidine	H	3,4,5 Trifluorophenyl	418
90	1-Piperidine	H	3,5 Dimethoxy-Phenyl	424
91	1-Piperidine	H	3-Nitrophenyl	409
92	1-Piperidine	H	3,4 Difluorophenyl	400
93	1-Piperidine	H	3,5 di-(trifluoromethyl)-Phenyl	500
94	1-Piperidine	H	3,4 Dimethoxyphenyl	424
95	1-Piperidine	H	4-Cyano-Phenyl	389
96	1-Piperidine	H	4-Ethylphenyl	392

97	1-Piperidine	H	3,5 Dichlorophenyl	433
98	1-Piperidine	H	3,5 Difluorophenyl	400
99	1-Piperidine	H	3-Bromophenyl	443
100	1-Piperidine	H	4-Butylphenyl	420
101	1-Piperidine	H	3-Cyanophenyl	389
102	1-Piperidine	H	2-Iodophenyl	490
103	1-Piperidine	H	Phenyl	364
104	1-Piperidine	H	4-Nitrophenyl	409
105	1-Piperidine	H	Trifluomethyl	356

-53-



Example 1066-amino-1-indanone t-butylcarbamate, 106

5 A mixture of 6-amino-1-indanone (4.41 g) and EtOAc (250 mL) was treated with di- t-butyl-di-carbonate (7.2 g) and the reaction stirred two days. After addition of K_2O_3 (4 g), the reaction was heated to 70 C over night. The mixture was cooled and treated with cold H_2O and extracted with EtOAc. The organics were washed with saturated aqueous citric acid and brine then the solvent was dried and evaporated to give a dark viscous oil that solidified. The material was further purified by hplc eluting with 20 % EtOAc-hexane to give a flocculant tan solid (5.1 g).

Example 1072-amino-6-t-butylcarbamido-indane, 107

15 A mixture of 106 (2.5 g), THF (75 mL), ammonia (25 mL), and Pt/C-S (0.9 g) was treated with H_2 at 1000 psi for 8 h at 140 C. The catalyst was removed by filtration and the solvent evaporated to give a foam that was purified by radial chromatography eluting with 20% EtOH-2%-NH₄H-CHCl₃ to give a white solid (0.9 g).

Example 1082-m-trifluoromethylbenzamido-6-t-butylcarbamido-indane, 108

25 A solution of 107 (0.9g) and a catalytic amount of 4-dimethylaminopyridine in pyridine (10 mL) was cooled in ice-water as m-trifluoromethylbenzoyl chloride (0.9 g) was added dropwise. The cooling was removed and the reaction was stirred over night. The solvent was evaporated, the residue treated with cold H_2O , and the mixture extracted with EtOAc. The extracts were washed with H_2O , 0.2 N HCl, H_2O , aqueous NaHCO₃, the solvent dried and then evaporated to give a white solid (1.42 g).

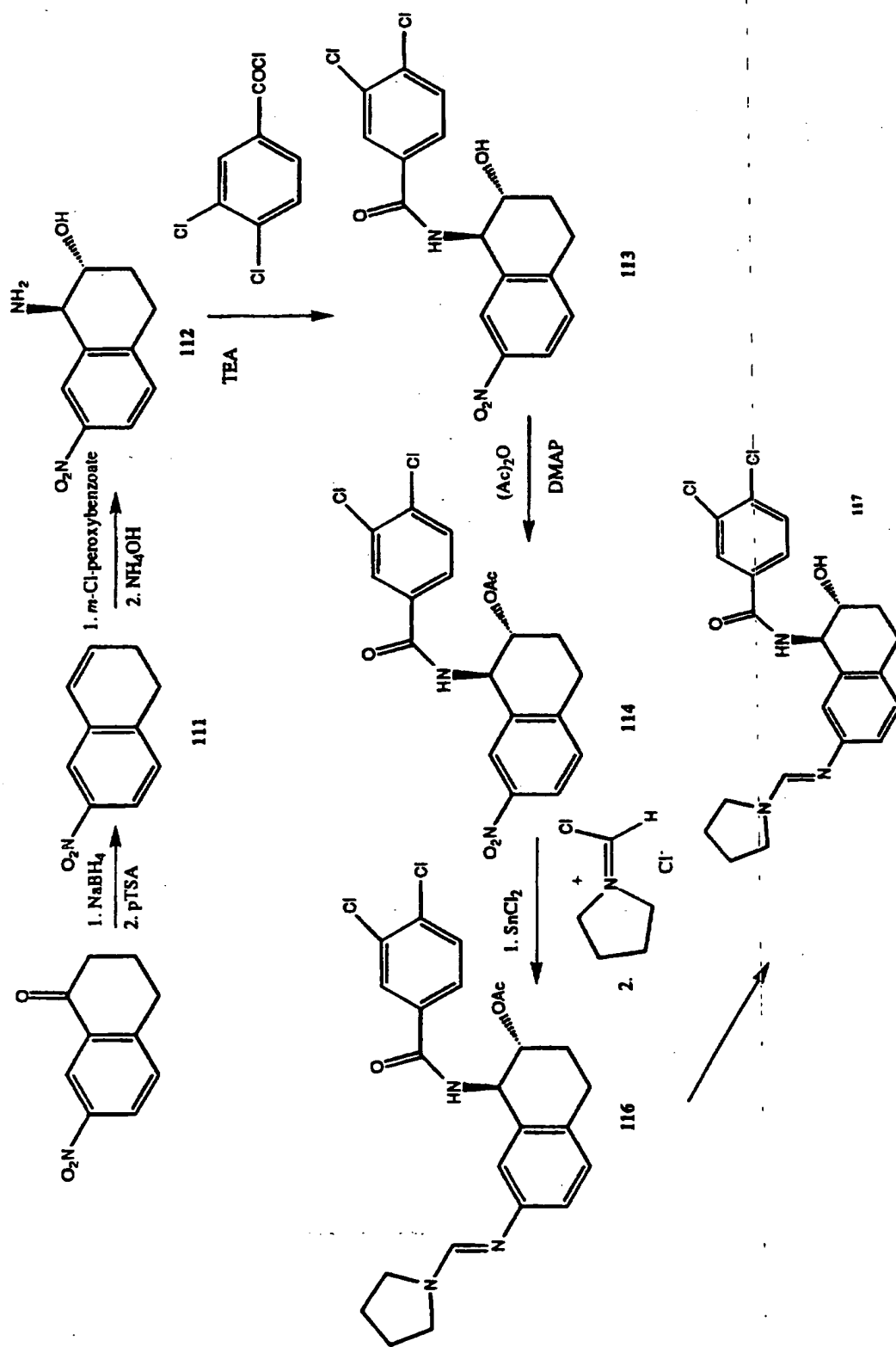
Example 1096-amino-2-m-trifluoromethylbenzamido-indane, 109

5 A solution of 108 (1.4 g) in EtOAc was cooled in ice-water
and treated with a stream of dry HCl for 2 min. After
another 10 min, the solvent was evaporated, the residue
suspended in cold water, and the mixture made basic. The
mixture was extracted with ether, the ether washed with
brine, the solvent then dried and evaporated to give a white
10 solid (1 g).

Example 1106-dimethylformamidino-2-m-trifluoromethylbenzamido-indane, 110

15 A mixture of chloromethylene-dimethylammonium chloride (0.1
g) and CH₂Cl₂ (5 mL) was treated with 109 (0.16 g). The
reaction was then treated with triethylamine (0.3 mL) and
after 5 min, the solvent was evaporated. The residue was
treated with ice-water, the mixture was acidified, and the
20 mixture extracted with ether. The aqueous phase was made
basic, the mixture was extracted with ether, and the extracts
washed with water and brine. The solvent was evaporated and
the residue purified by radial chromatography eluting with
10% EtOH-CHCl₃. The HCl salt crystallized from EtOAc-acetone
25 as a white solid (70 mg), m.p. 239 C, dec.

-56-



Example 111

6-nitro-1,2-dihydronaphthalene, 111

5 A suspension of 7-nitrotetralone (20 g, 0.105 mol) in MeOH
(300 mL) was treated with NaBH₄ (4.1 g) with intermittent
cooling. After the addition, cooling was removed and the
reaction stirred over night. The reaction was cooled in ice-
water and quenched with a solution of MeOH (200 mL) and
concentrated HCl (35 mL). The solvent was evaporated, the
10 residue was suspended in H₂O, and the mixture was extracted
with CHCl₃. The extracts were dried and the solvent
evaporated to give a tan solid. A mixture of the solid, p-
toluenesulfonic acid (0.4 g), and toluene (300 mL) was heated
to reflux for over night with water being collected in a
15 Dean-Stark trap. The reaction was cooled, washed with B₂
aqueous NaHCO₃, and brine, then the solvent was dried and
evaporated to give a dark liquid (15.6 g) that had an nmr
consistent with the desired material.

20

Example 112(±) -trans-1-amino-2-hydroxy-7-nitrotetraline, 112

A solution of 111 (15.6 g) in CH₂Cl₂ (400 mL) was cooled in
ice-water and m-chloro-peroxybenzoic acid (42 g of 50-55%
25 pure material) was added in portions over 1 h. Excess
oxidant was then destroyed with aqueous sodium thiosulfate.
The reaction was filtered and the organics washed with
aqueous NaHCO₃ and brine, then the solvent was dried and
evaporated to give a yellow solid (16.9 g). The solid was
30 suspended in ammonium hydroxide (550 mL) and the mixture
heated to 55 °C for 72 h. The solid was collected by
filtration and recrystallized from MeOH to give a flocculant
white solid, m.p. 216-218 °C (12.3 g).

Example 113(±) -trans-1-(3,4-dichlorobenzamido)-2-hydroxy-7-nitrotetraline, 113

5 A solution of 112 (2.1 g) in warm THF (300 mL) was treated with triethylamine (5 mL) and the solution allowed to come to room temperature. A solution of 3,4-dichlorobenzoyl chloride (2.3 g) in THF (50 mL) was added dropwise over 20 min. After stirring over night, the solvent was evaporated to give a
10 solid (3.97 g) that had the appropriate nmr spectrum.

Example 114(±) -trans-1-(3,4-dichlorobenzamido)-2-acetoxy-7-nitrotetraline, 114

15 A mixture of 113 (1.9 g, 0.005 mol) in THF (200 mL), triethylamine (1.3 mL), and a catalytic amount of 4-dimethylaminopyridine was treated with acetic anhydride (0.9 mL). After stirring over night, the solvent was evaporated
20 and the residue treated with H₂O. After 2 h, the mixture was extracted with EtOAc. The extracts were washed with 1 N H₂SO₄, brine, aqueous NaHCO₃, and brine, then the solvent was dried and evaporated to give a flocculant white solid (1.94 g) that had the appropriate nmr for the desired material.

25

Example 115(±) -trans-1-(3,4-dichlorobenzamido)-2-acetoxy-7-aminotetraline, 115

30 A solution of 114 (1.9 g) in DMF (100 mL) was treated with SnCl₂·2H₂O (4 g). After 4 h, additional SnCl₂·2H₂O (1 g) was added three times over three days. The solvent was then evaporated, the residue suspended in H₂O-EtOAc, the mixture neutralized with 5N NaOH, and the mixture filtered. The
35 organics were separated, washed with brine, dried, and the solvent evaporated to give a brown foam (1.9 g).

Example 116(±) -trans-1-(3,4-dichlorobenzamido)-2-acetoxy-7-(pyrrolidinoformamido)tetraline, 116

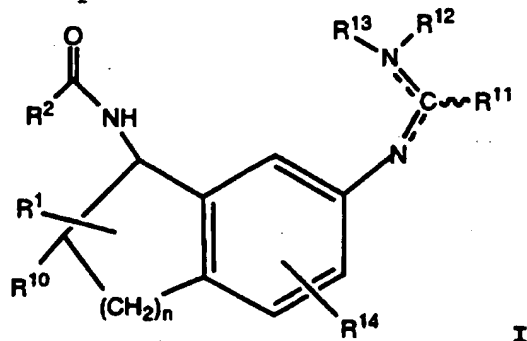
5 A solution of pyrrolidine carboxamide (1.5 mL) in CH_2Cl_2 (25 mL) was treated with POCl_3 (0.23 mL). After 1.5 h, the solution was treated with triethylamine (1 mL) and 115 (0.5 g). After stirring over night, the solvent was evaporated, the residue was treated with ice-water, the mixture
10 neutralized, and the mixture extracted with EtOAc. The extracts were washed with brine and the solvent was dried and evaporated to give a dark oil. The oil was purified by radial chromatography eluting with 5% EtOH- CHCl_3 to give a tan solid that was recrystallized from EtOAc to give a white
15 solid (0.18 g), m.p. 229 °C, dec.

Example 117(±) -trans-1-(3,4-dichlorobenzamido)-2-hydroxy-7-(pyrrolidinoformamido)tetraline, 117

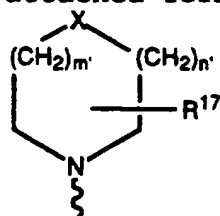
20 A solution of 116 (0.27 g) in MeOH (10 mL) was treated with 0.135 M sodium methoxide (4.9 mL) in MeOH. After 4 h, the solvent was evaporated, the residue was suspended in Et_2O , and the solid was collected by filtration. The solid was
25 crystallized from EtOAc-ether to give a tan powder, m.p. 206-208 °C.

We claim:

1. A compound of the Formula I:



- 5 R^1 is selected from the group consisting of hydrogen, $-OR^4$, $-SR^5$, C_1 - C_3 alkyl, C_2 - C_3 alkenyl, halo, $-CN$, $S(O)_{m2}$, $-COR^{4b'}$, and $-OC(O)-R^{15}$;
- $m2$ is from 0 to 2;
- 10 R^2 is selected from the group consisting of C_1 - C_{10} alkyl, substituted C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, substituted C_2 - C_{10} alkenyl, C_3 - C_8 cycloalkyl, substituted C_3 - C_8 cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic;
- R^4 is hydrogen, C_1 - C_3 alkyl;
- 15 R^5 is hydrogen, C_1 - C_3 alkyl;
- R^{10} is selected from the group consisting of hydrogen, carbonyl, halo, and C_1 - C_3 alkyl;
- R^{11} is selected from the group consisting of hydrogen and C_1 - C_3 alkyl;
- 20 R^{12} is independently selected from the group consisting of hydrogen, C_1 - C_{10} alkyl, and aryl;
- R^{13} is independently selected from the group consisting of hydrogen, C_1 - C_{10} alkyl, and aryl; or
- R^{12} and R^{13} together with the nitrogen to which they are
- 25 attached form a group of the formula II:



II; or

-61-

II' wherein the II' group is a group of Formula II which is unsaturated; or
R¹¹ and R¹² together with the nitrogen and carbon to which they are bound can join to form a three to six membered ring;
5 R¹⁴ is selected from the group consisting of H, halo, C₁-C₃ alkyl, S(O)_{m3} and -OR¹⁶;
R¹⁵ is C₁-C₃ alkyl or aryl;
R¹⁶ is C₁-C₃ alkyl;
R¹⁷ is independently selected from the group consisting of
10 hydrogen, -OR^{4'}, -SR^{5'}, C₁-C₃ alkyl, C₂-C₃ alkenyl, halo, -CN, S(O)_{m2}, -COR^{4b}, and -OC(O)-R^{15'};
R^{4b} and R^{4b'} are each independently selected from hydrogen and C₁-C₃ alkyl;
R^{15'} is C₁-C₃ alkyl or aryl;
15 m₂' is 0 to 2;
R^{4'} is hydrogen, C₁-C₃ alkyl;
R^{5'} is hydrogen, C₁-C₃ alkyl;
m₂ is 0 to 2;
X is selected from the group consisting of C, O, S, N,
20 carbonyl, and a bond;
n' is 0 to 2;
m' is 0 to 2;
m₃ is 0 to 2;
n is 0 to 3; or
25 a pharmaceutically acceptable salt or solvate thereof.

2. A compound of **Claim 1** wherein n is 1.

3. A compound of **Claim 2** wherein R¹ is OH.

4. A compound of **Claim 2** wherein R² is 3,4 dicloro substituted phenyl.

5. A compound of **Claim 2** wherein R² is meta trifluoromethyl substituted phenyl.

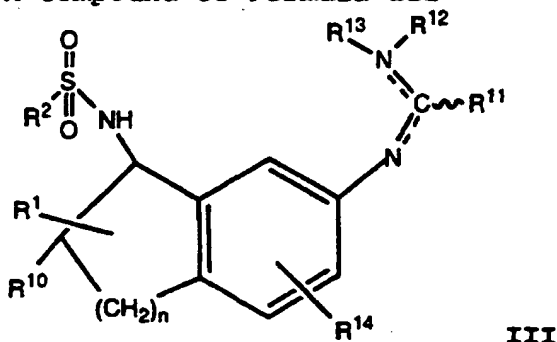
6. A compound of **Claim 4** wherein R¹ is OH.

7. A compound of **Claim 5** wherein R^1 is OH.
8. A compound of **Claim 2** wherein R^2 is a bicyclic aryl group.
- 5 9. A compound of **Claim 7** wherein R^2 is naphthyl.
- 10 10. A compound of **Claim 2** wherein the compound is *trans*.
11. A compound of **Claim 2** wherein R^{12} and R^{13} together with the nitrogen to which they are attached form a piperidine ring.
- 15 12. A compound of **Claim 2** wherein formula **II** is a pyrrolidine ring.
13. A compound of **Claim 2** wherein R^{12} and R^{13} are each independently selected from C_1 - C_3 alkyl.
- 20 14. A compound of **Claim 13** wherein R^2 is biphenyl.
15. A compound of **Claim 1** wherein n is 2.
- 25 16. A pharmaceutical formulation comprising a compound of **Claim 1** and one or more pharmaceutically acceptable excipients therefor.
- 30 17. A method for treating a mammal suffering from or susceptible to a psychotic condition comprising administering to said mammal an effective amount of a compound of **Claim 1**.
- 35 18. A method for treating a mammal suffering from or susceptible to a condition which is associated with the mediation of a muscarinic receptor, comprising administering to said mammal an effective amount of a compound of **Claim 1**.

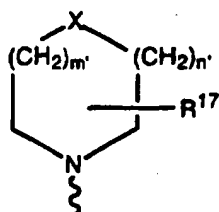
19. A method for treating a mammal suffering from or susceptible to a condition which can be treated using a muscarinic receptor agonist, comprising administering to said mammal an effective amount of a compound of **Claim 1**.

5

20. A compound of Formula **III**



- R^1 is selected from the group consisting of hydrogen, $-OR^4$, $-SR^5$, C_1 - C_3 alkyl, C_2 - C_3 alkenyl, halo, $-CN$, $S(O)_{m2}$, $-COR^{4b'}$, and $-OC(O)-R^{15}$;
- $m2$ is from 0 to 2;
- R^2 is selected from the group consisting of C_1 - C_{10} alkyl, substituted C_1 - C_{10} alkyl, C_2 - C_{10} alkenyl, substituted C_2 - C_{10} alkenyl, C_3 - C_8 cycloalkyl, substituted C_3 - C_8 cycloalkyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, heterocyclic, and substituted heterocyclic;
- R^4 is hydrogen, C_1 - C_3 alkyl;
- R^5 is hydrogen, C_1 - C_3 alkyl;
- R^{10} is selected from the group consisting of hydrogen, carbonyl, halo, and C_1 - C_3 alkyl;
- R^{11} is selected from the group consisting of hydrogen and C_1 - C_3 alkyl;
- R^{12} is independently selected from the group consisting of hydrogen, C_1 - C_{10} alkyl, and aryl;
- R^{13} is independently selected from the group consisting of hydrogen, C_1 - C_{10} alkyl, and aryl; or
- R^{12} and R^{13} together with the nitrogen to which they are attached form a group of the formula **II**:



II; or

II' wherein the II' group is a group of Formula II which is unsaturated; or

R¹¹ and R¹² together with the nitrogen and carbon to which they are bound can join to form a three to six membered ring; R¹⁴ is selected from the group consisting of H, halo, C₁-C₃ alkyl, S(O)_{m3} and -OR¹⁶;

R¹⁵ is C₁-C₃ alkyl or aryl;

R¹⁶ is C₁-C₃ alkyl;

R¹⁷ is independently selected from the group consisting of hydrogen, -OR^{4'}, -SR^{5'}, C₁-C₃ alkyl, C₂-C₃ alkenyl, halo, -CN, S(O)_{m2'}, -COR^{4b}, and -OC(O)-R^{15'};

R^{4b} and R^{4b'} are each independently selected from hydrogen and C₁-C₃ alkyl;

R^{15'} is C₁-C₃ alkyl or aryl;

m_{2'} is 0 to 2;

R^{4'} is hydrogen, C₁-C₃ alkyl;

R^{5'} is hydrogen, C₁-C₃ alkyl;

m₂ is 0 to 2;

X is selected from the group consisting of C, O, S, N, carbonyl, and a bond;

n' is 0 to 2;

m' is 0 to 2;

m₃ is 0 to 2;

n is 0 to 3; or

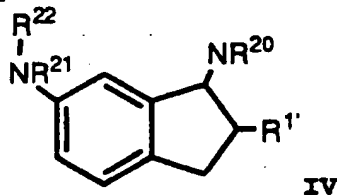
a pharmaceutically acceptable salt or solvate thereof.

21. A formulation comprising a compound of Claim 20 and one or more pharmaceutically acceptable excipients or carriers therefor.

22. A method for treating a condition associated with the modulation of a muscarinic receptor comprising administering an effective amount of a compound of **Claim 20** to a mammal in need of such treatment.

5

23. A compound of Formula **IV**



R²¹ and R²² are selected from H and O;

R²⁰ is selected from amine protecting groups;

10 R^{1'} is selected from the group consisting of -OR⁴, -SR⁵, C₁-C₃ alkyl, C₂-C₃ alkenyl, halo, -CN, S(O)_{m2}, -COR^{4b'}, and -OC(O)-R¹⁵;

m₂ is 0 to 2;

15 R⁴ and R^{4b'} are each independently selected from hydrogen and C₁-C₃ alkyl;

R⁵ is selected from hydrogen and C₁-C₃ alkyl;

R¹⁵ is C₁-C₃ alkyl or aryl;

or

a pharmaceutically acceptable salt or solvate thereof.

20

24. A compound of **Claim 23** wherein R²¹ and R²² are each O.

25 25. A compound of **Claim 24** wherein R²⁰ is a carbamate.

26. A compound of **Claim 25** wherein R²⁰ is BOC.

30 27. A compound of **Claim 23** wherein R²¹ and R²² are each H.

28. A compound of **Claim 27** wherein R²⁰ is a carbamate.

29. A compound of **Claim 28** wherein R^{20} is BOC.

30. A compound of **Claim 28** wherein $R^{1'}$ is OH.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/00997

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Extra Sheet.

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CASONLINE SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	JP 61-60610 A (SAKA OTSUKA PHARM CO. LTD.) 28 March 1986, page 59, column 2 and page 69 column 1.	23-30
Y	OSHIRO et.al., Novel Cerebroprotective Agents With Central Cervous System Stimulating Activit. 1. Synthesis and Pharmacology of 1- Amino 7-Hydroxyindan Derivatives, J. Med. Chem., 1991, Vol 34, No. 7, pages 2005-2006.	23-30
A	WO 95/18617 A1 (TEVA PHARMACEUTICAL INDUSTRIES LTD.) 13 July 1995.	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

02 MAY 1997

Date of mailing of the international search report

09 JUN 1997

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

SHAIENDRA KUMAR

Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/00997

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☒ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US97/00997

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (6):

A61K 31/18, 31/34, 31/38, 31/44, 31/165, 31/275, 31/445;

C07C 233/65, 255/50, 311/01;

C07D 207/06, 211/06, 213/16, 333/10, 333/52, 401/02

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

514/319, 343, 354, 355, 438, 443, 444, 448, 522, 523, 524, 604, 618, 622;

546/162, 206, 281, 314, 315, 316;

548/566, 567, 568;

549/57, 72; 564/80, 92, 93, 162

B. FIELDS SEARCHED

Minimum documentation searched

Classification System: U.S.

514/319, 343, 354, 355, 438, 443, 444, 448, 522, 523, 524, 604, 618, 622;

546/162, 206, 281, 314, 315, 316;

548/566, 567, 568;

549/57, 72; 564/80, 92, 93, 162

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claim(s) 1-19, drawn to carboxamide compounds, composition and method of use.

Group II, claim(s) 20-22, drawn to sulfonamide compounds, composition and method of use.

Group III, claim(s) 23-30, drawn to amino or nitro containing compounds.

The inventions listed as Groups I through III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: Group I compounds are carboxamides, Group II compounds are sulfonamides and Group III compounds are amino or nitro containing compounds. The three groups having three different functional groups, provide special technical feature to the composition which is not the same for each composition and foreshadows the common special technical feature common to all the three groups, i.e., indane group. As pointed out above, carboxamide, sulfonamide and amino/or nitro groups are functionally different and hence lack special technical feature. A reference anticipating compounds of Group I, may not be a reference to Group II or Group III, again because of three chemically distinct disparate groups (37 CFR 1.475(d)).

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